
# Welcome to the 2017 Annual Report

"The NTP serves a critical role for our nation. It provides a unique, consolidated venue for toxicology research, testing, and analysis to occur." – Dr. Linda Birnbaum, NTP Director

Read the 2017 Letter from the NIEHS and NTP Director.


## FY 2017 at a Glance

- Completed NTP Reports
- Fifty Years of NIEHS Captured in History and Science Collections
- 14th Report on Carcinogens Released

More

## Learn About Us

- Mission and Goals
- Organizational Structure and Oversight
- Funding
- Program Contact Information

More

## Scientific and Public Input Opportunities

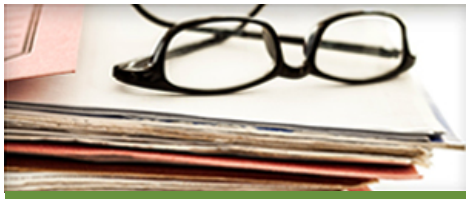
- Nominations
- NTP Board of Scientific Counselors
- SACATM

More

## Research and Testing

- Tox21
- Testing and Toxicology Studies
- NICEATM
- ICCVAM

More



## Literature Analysis

- Noncancer Research
- Report on Carcinogens

## Partner Agency Research

- About NTP at NIEHS
- NTP at NCTR
- NTP at NIOSH



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Director of Office of Liaison, Policy, and Review and Editor-in-Chief: Mary Wolfe | Managing Editor: Joshua Cleland (ICF)

# Letter from the NIEHS and NTP Director

In fiscal year (FY) 2017, NTP continued to advance toxicology and inform public health policy by providing information to decision makers and the public about substances in our environment. Numerous studies were published on substances of public health concern, such as flame retardants, metals, and widely used industrial chemicals. Among these is the first study to investigate occupational exposure to bisphenol A by manufacturing workers in the United States.

NTP engaged in several activities to advance alternatives to animal testing. The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods sponsored several venues to receive stakeholder input on a draft Strategic Roadmap toward new approaches to safety evaluation of chemicals and medical products. In addition, the “Tox21” initiative worked to develop high-throughput 3D tissue culture models that mimic the functionality of specific organ tissues to predict responses to environmental exposures.

The NTP Office of the Report on Carcinogens held a workshop to obtain external scientific input on topics important for informing their literature-based cancer hazard assessments for shift work at night, light at night, and circadian disruption.

The NTP Office of Health Assessment and Translation published the NTP Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate. This evaluation was the first to reach hazard conclusions using the new systematic-review approach for study assessment and evidence integration.

I invite you to read this report to learn about what we accomplished in FY 2017 to safeguard public health by informing policy with the best science.

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.

Dr. Birnbaum has served as the Director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) since 2009

(Photo courtesy of Steve McCaw)

# FY 2017 at a Glance

## Completed NTP Reports

NTP studies are published in an NTP report series after undergoing peer review. NTP reports published in FY 2017 or expected for peer review in FY 2018 are listed.


## Timeline of Events

Highlighted NTP activities in FY 2017.


## Fifty Years of NIEHS Captured in History and Science Collections

NIEHS catalogs hundreds of mementos and artifacts to commemorate its golden anniversary.


## 14th Report on Carcinogens Released

NTP released the 14th Report on Carcinogens in FY 2017.


## Kleinstreuer Receives Lush Prize Young Researcher Award

NTP computational toxicologist Nicole Kleinstreuer, Ph.D., was recognized for her work toward eliminating animal use for chemical safety testing.

## NTP Supports First Study of BPA Levels in U.S. Factory Workers

NIOSH researchers found elevated BPA levels in workers' urine.

## New Cell Models for Toxicology Better Mimic Human Tissue

For use in high-throughput toxicity testing, the new models can quickly and reliably identify environmental toxins linked to human disease.

## ICCVAM Adds a New Member Agency

The National Institute of Standards and Technology brings expertise in process controls, measurement artifacts, and interlaboratory testing.

## NTP Archives Supports Global Cancer Research Initiatives

NTP is contributing rodent tumor and normal samples to a new $24.4 million study of the links between human cancers and specific environmental factors.


## Public Forum on Alternatives to Animal Testing Highlights Next Steps

Attendees learned about and discussed new approaches into safety testing of chemicals and medical products in the United States.

## New NTP Website Getting Rave Reviews

The visually appealing new site offers many new tools to facilitate navigation and usability.

## At 10 Years, Tox21 Continues to Drive Toxicity Testing Forward

The Tox21 program has a 10-year track record of developing cutting-edge technology to better assess chemical toxicity in humans.


## NTP Public Health Impact on Regulatory Agencies

Federal and state regulatory agencies use NTP study data and recommendations when considering the need to test and regulate specific chemicals to protect human health.

## Additional Activities

Additional meetings with stakeholders and the scientific community in which NTP participated.

## Publications

Full citations for NTP reports, journal publications, and book chapters published during FY 2017.

# Completed NTP Reports

The findings of NTP studies and research projects are published in three types of NTP reports.

- NTP Technical Reports document long-term toxicology and carcinogenicity studies, generally of 2 years' duration.
- Toxicity Reports document shorter-term studies, generally up to 13 weeks' duration.
- NTP Research Reports provide the results of research studies, rapid communications, and literature surveys that do not fall under the scope of the first two report series.

All published NTP reports are peer reviewed by experts who are screened for conflicts of interest prior to their service. NTP reports completed in FY 2017, and in prior years, are available on the NTP website and catalogued in PubMed.

## Technical Reports Published During FY 2017 Reporting Levels of Evidence of Carcinogenic Activity

NTP Technical Reports published in FY 2017 are listed below. NTP used established criteria to evaluate the findings and determine the strength of evidence for conclusions regarding the carcinogenic activity of each substance. The conclusions for level-of-evidence of carcinogenic activity are included.

| Chemical | Technical Report Number (CASRN*) | Use | Evidence of Carcinogenic Activity | | | |
|---|---|---|---|---|---|---|
| | | | Male Rats | Female Rats | Male Mice | Female Mice |
| Indole-3-Carbinol | TR-584 (700-06-1) | Natural component of brassica vegetables; marketed as a dietary supplement and cancer preventive agent | No evidence | Some evidence | Clear evidence | No evidence |
| TRIM® VX | TR-591 (NA) | Metalworking fluid used as a lubricant and coolant liquid and for cleaning tools and parts during cutting, drilling, milling, and grinding | Equivocal evidence | Equivocal evidence | Clear evidence | Clear evidence |

*CASRN = Chemical Abstracts Service Registry Number

## Technical Reports that Underwent Peer Review in FY 2017

Three draft technical reports, listed below, underwent peer review in FY 2017. The NTP website provides further information about these and other past technical reports peer review meetings.

| Chemical | Technical Report Number (CASRN*) | Use | Report Conclusions as Written and Panel Vote |
|---|---|---|---|
| 2,3-Butanedione | TR-593<br>(431-03-8) | Used in artificial flavor formulations, such as microwave popcorn, cake mixes, flour, beer, wine, margarine, cheese, candy, crackers, cookies, ice cream, and many others food and beverage products. | "Exposure to 2,3-butanedione resulted in increased incidences of nonneoplastic lesions of the nose, larynx, trachea, lung, and eye in male and female rats and mice."<br>4 yes, 2 no, 0 abstentions<br>Panelists who voted "no" recommended clear evidence of carcinogenic activity for male rats and some evidence of carcinogenic activity for female mice. |
| p-Chloro-α,α,α-trifluorotoluene | TR-594<br>(98-56-6) | Solvent used in paints and coatings and as an industrial intermediate in the production of other chemicals (e.g., herbicides, dyes, pharmaceuticals). | "Exposure to p-chloro-α,α,α-trifluorotoluene caused increased incidences of nonneoplastic lesions in the lung and liver of male and female rats and mice, in the nose of male rats, in the adrenal medulla and uterus of female rats, in the forestomach of male and female mice, and in the larynx in male mice. Exposure to p-chloro-α,α,α-trifluorotoluene caused increased severity of nonneoplastic lesions in the kidney of male rats."<br>6 yes, 0 no, 0 abstentions |
| Zinc, dietary | TR-592<br>(5263-02-5) | Used in a wide range of industries including rubber production, animal feed supplement, fertilizer additive, cosmetics, drugs, paint pigment, dental cements, wood preservatives, batteries, galvanizing and metal work, textile production, television screens, watches, and smoke bombs. | "Exposure to diets containing excess zinc resulted in increased incidences of nonneoplastic lesions of the pancreas in male and female rats. Exposure to diets deficient in zinc resulted in increased incidences of nonneoplastic lesions of the testes in male rats."<br>6 yes, 0 no, 0 abstentions |

*CASRN = Chemical Abstracts Service Registry Number

## Toxicity Reports Published During FY 2017

NTP Toxicity Reports evaluate and characterize the toxicological potential of a substance under study conditions. NTP Toxicity Reports published in FY 2017 are listed below.

| Chemical | Toxicity Report Number (CASRN*) | Use |
|---|---|---|
| o-Chloropyridine | TOX-83<br>(109-09-1) | Intermediate in synthetic organic, pharmaceutical, and agricultural chemical (fungicides, herbicides) manufacture. Also used as a catalyst for phase transfer and is a key intermediate in the manufacture of pyrithione-based biocides for use in cosmetics and various pharmaceutical products. |
| Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) | TOX-85<br>(21850-44-2) | Flame retardant in electronics, building and construction materials, and automotive materials. |

*CASRN = Chemical Abstracts Service Registry Number

## Research Reports Published During FY 2017

The NTP Research Report series was launched in FY 2016 to promote transparency and reproducibility. The series strengthens the science base and provides information useful for public health decision-makers. NTP Research Reports published in FY 2017 are listed below.

| Report Title | Research Report Number |
|---|---|
| Absence of Formaldehyde-Induced Neoplasia in Trp53 Haploinsufficient Mice Exposed by Inhalation | RR-03 |

# FY 2017 Timeline

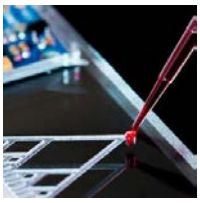
November 2016


**14th Report on Carcinogens Released**
The newly updated Report on Carcinogens released November 3 includes listings for seven substances: five viruses, trichloroethylene, and cobalt and cobalt compounds.

December 2016

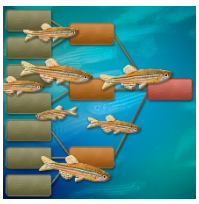
**NTP Board of Scientific Counselors Meeting**
The December 14–15 Board of Scientific Counselors meeting featured ongoing research collaborations between NTP partner agencies. From exploring the organisms in our gut to documenting chemical exposures in the workplace, the partnerships are proving to be productive scientific collaborations.

January 2017



**NICEATM Communities of Practice Webinar**
On January 24, NICEATM presented a webinar on cheminformatics techniques for 21st Century Toxicity Testing.

February–March 2017



**NICEATM Webinar Series**
NICEATM hosted a series of three webinars in February through March on the use of informatics to improve data analysis of chemical screening assays conducted in zebrafish.

May 2017


**ICCVAM Public Forum**
The lead topic of an ICCVAM Public Forum on May 23 was A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States.

June 2017


**BioMed21 – A Human Pathway-based Approach to Disease and Medicine Workshop**
This workshop, co-organized by NICEATM and the Human Toxicology Project Consortium, assembled experts to identify barriers and opportunities and to recommend the needs for achieving implementation of a human systems-biology platform to understand disease and improve interventions.

June 2017

**NTP Board of Scientific Counselors Meeting**
At its June 29 meeting, the NTP Board of Scientific Counselors reviewed and enthusiastically supported NTP's progress in researching human exposure to chemical mixtures.

July 2017

**Report on Carcinogens Peer Review Panel**
A panel convened by NTP on July 24 recommended listing in the Report on Carcinogens six compounds known as haloacetic acids as reasonably anticipated to be carcinogens. The compounds are byproducts created when chlorine, chloramine, or chlorine dioxide are used to disinfect drinking water.

July 2017

**NTP Technical Report Peer-Review Panel**
The NTP scientific panel convened on July 13 and reviewed and accepted draft technical reports on the carcinogenicity and toxicity of three substances: 2,3-butanedione (used to flavor microwave popcorn and other foods), dietary zinc, and PCTFT (p-chloro-α,α,α-trifluorotoluene, an industrial solvent).

August 2017


**Symposium on Systematic Review**
On August 24–25, NTP hosted the 4th International Symposium on Systematic Review and Meta-analysis of Laboratory Animal Studies. Experts from Europe, Egypt, India, Australia, North America, and South America participated.

September 2017


**SACATM Meeting**
At its September 18–19 meeting, SACATM provided advice on A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States then in development by ICCVAM.

# Fifty Years of NIEHS Captured in History and Science Collections


To commemorate its golden anniversary year, NIEHS staff searched, collected, sorted, identified, and cataloged hundreds of mementos and artifacts to record and preserve the institute's history. The NIEHS Office of Communications and Public Liaison assembled the material into multimedia collections now available on the NIEHS 50th Anniversary webpages.

Photographs, an interactive timeline of scientific milestones, oral histories, and testimonial reflections on the institute's impact have been restored, digitized, and organized for easy viewing. Other keepsakes that could not be digitized for the online collections have been stored in a time capsule at the NIEHS facility in Research Triangle Park, North Carolina.

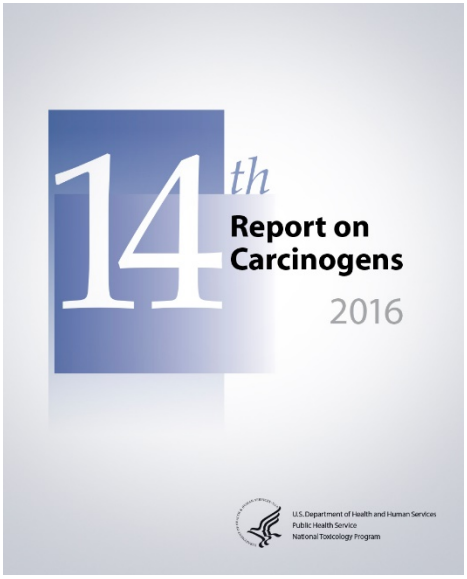
The NIEHS Reflections page has news clips, oral histories, and early issues of the institute's newsletter, Environmental Factor. The page features a personal tribute to NIEHS, written by environmental toxicologist, Bernard Goldstein, M.D., professor emeritus and former dean of the University of Pittsburgh Graduate School of Public Health.

Audio files of oral histories from scientists and institute leaders have been posted on the page, and 50 years of institute history and scientific progress, including the following, can be explored:

- Highlights of environmental health science research, such as discovery of the link between asbestos and mesothelioma.
- New programs, including the autism research network.
- Institutional developments, from creation of the National Toxicology Program to information on institute directors.

The NIEHS communications team collected photos from retirees, current employees, archives, and long-forgotten boxes and file folders. Most are available to the public on the Photo Gallery page of the anniversary website. Posed or informal, artistic or candid, the snapshots provide glimpses of institute researchers, facilities, and team-building activities across the years.

# 14th Report on Carcinogens Released




The U.S. Department of Health and Human Services released the 14th Report on Carcinogens November 3, 2016. The congressionally mandated report, which NTP prepares, included seven newly reviewed substances, bringing the total to 248 listings.

The Report on Carcinogens lists a variety of environmental factors, collectively called substances and grouped into two categories: known to be a human carcinogen and reasonably anticipated to be a human carcinogen. The listings can include chemicals; mixtures of chemicals; infectious agents, such as viruses; and physical agents, such as X-rays and ultraviolet radiation.

The seven newly reviewed substances added to the 2016 Report are listed below.

| Substance | Listing Status | Description |
|---|---|---|
| Trichloroethylene (TCE) | Known to be a human carcinogen | Industrial solvent |
| Cobalt and cobalt compounds that release cobalt ions in vivo | Reasonably anticipated to be a human carcinogen | Metal and its compounds |
| Human immunodeficiency virus type 1 (HIV-1) | Known to be a human carcinogen | Virus |
| Human T-cell lymphotropic virus type 1 (HTLV-1) | Known to be a human carcinogen | Virus |
| Epstein-Barr virus (EBV) | Known to be a human carcinogen | Virus |
| Kaposi sarcoma-associated herpesvirus (KSHV) | Known to be a human carcinogen | Virus |
| Merkel cell polyomavirus (MCV) | Known to be a human carcinogen | Virus |

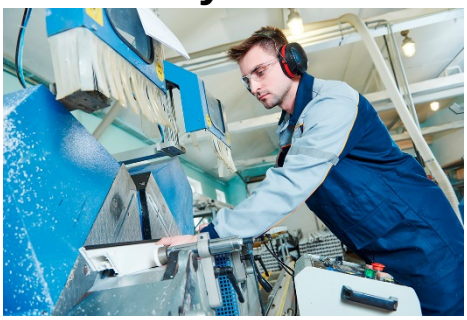
# Kleinstreuer Receives Lush Prize Young Researcher Award

NTP computational toxicologist Nicole Kleinstreuer, Ph.D., was recognized for her work toward eliminating animal use for chemical safety testing. The Lush Cosmetics Young Researcher—Americas Prize, one of the annual Lush Prizes honoring such progress, was presented during a November 2, 2016, ceremony at the Lush Cosmetics North American headquarters in Vancouver, British Columbia.

Kleinstreuer, deputy director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, was awarded the prize for developing computational toxicity models for predicting outcomes such as developmental toxicity, endocrine disruption, and skin sensitization. Kleinstreuer said she hopes that some of the company's data from human testing could be used in the models to predict skin sensitization. Using human data could improve the accuracy of model predictions.

The Lush Young Researcher Prize is only the latest honor for Kleinstreuer and the center, as they apply modern methods and technologies to chemical safety testing. Kleinstreuer hopes this award brings attention and support to the center's current focus, working with U.S. and international regulatory agencies to replace animal use worldwide in testing for skin and eye irritation, acute toxicity, and skin sensitization.

# NTP Supports First Study of BPA Levels in U.S. Factory Workers



A new study supported by NTP was the first to investigate occupational exposure to BPA (bisphenol A) among manufacturing workers in the United States. Researchers at NIOSH led the study, which appeared January 1, 2017, in the journal "Annals of Work Exposures and Health." NIOSH is a member agency of NTP, and the study was conducted as part of an ongoing collaboration between the two agencies.

The NIOSH study included six U.S. companies that make BPA or manufacture or use resins and waxes containing BPA. Of the 78 workers participating in the study, most were white males. Over two days, participants provided seven urine samples. The participants also answered questions about food and beverage products they consumed in the previous 24 hours.

Researchers at the Centers for Disease Control and Prevention (CDC) have found BPA in the urine of nearly all people tested, indicating widespread exposure in the U.S. population. Diet is thought to be the main nonoccupational source of BPA exposure. Workers who participated in the new study handled raw BPA, often in large quantities, and—unlike the general population—were exposed to BPA mainly by inhalation and absorption through the skin.

NIOSH researchers found that BPA levels in the urine of workers were, on average, about 70 times higher than that of most adults in the United States. Certain job categories were associated with average urine levels more than 300 times greater than in the general population. Workers who handled sacks of BPA and carried process or bulk samples containing BPA for quality control testing, for example, had increased urinary BPA levels. Among the highest exposed workers were those who worked with molten casting wax that contained BPA. The lowest urinary BPA levels (trace amounts) were found in workers who handled a resin product. The study did not evaluate the health of the participating workers.

The NIOSH Science Blog provides more information about this study and ways to reduce exposure.

# New Cell Models for Toxicology Better Mimic Human Tissue

NTP researchers are developing cell models that better mimic the structure and function of human tissue for use in high-throughput toxicological testing. The effort is part of the Tox21 initiative to move away from animal testing. Advanced tissue culture models can quickly and reliably identify environmental toxins linked to human disease.

Sreenivasa Ramaiahgari, Ph.D., an NTP postdoctoral fellow, described his work on refining cell models during a January 13, 2017 talk at the Duke University Integrated Toxicology and Environmental Health Program seminar series. Ramaiahgari works in the NTP Biomolecular Screening Branch, the NTP lead for Tox21. His talk, “Organotypic In Vitro Models for Studying Chemical-induced Effects,” described his research involving three-dimensional organotypic models—models that behave like living tissue—of liver, kidney, and cancer cells.

Ramaiahgari developed a liver model using progenitor cells, a type of stem cell that can be induced to differentiate into other cell types, including liver cells. Ramaiahgari also developed organotypic tissue models for breast and prostate cell types. These models display tissue-specific functionalities not observed with conventional tissue culture models.

Ramaiahgari’s goal at NTP is to develop organotypic tissue culture models for all tissue types—liver, kidney, lung, heart, breast, neuronal, intestinal, and others—for application in predictive toxicology using high-throughput testing.

# ICCVAM Adds a New Member Agency

In early 2017, the National Institute of Standards and Technology (NIST) joined the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). NIST participation brings experience to the committee in the study of process controls, measurement artifacts, and interlaboratory testing.

Supported by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, the committee was established to facilitate and promote development and regulatory acceptance of new toxicological tests that could replace, reduce, or refine animal use. The expertise within NIST benefits the committee, especially in developing validation studies to assess the appropriateness of new test methods for specific purposes. In particular, NIST has experience with cell-based and small model organism assays, which are becoming increasingly important as alternatives for traditional animal tests. NIST also brings expertise in experimental design and statistical analysis.

This event represents the first time the committee has expanded its membership since its inception in 2000. NIST, part of the U.S. Department of Commerce, has been interacting with the committee since 2015. The agency submitted an official request to join in January 2017, which NIEHS Director Linda Birnbaum approved in February 2017.

# NTP Archives Supports Global Cancer Research Initiatives


The NTP Archives is contributing rodent tumor and normal samples to a new $24.4 million study to investigate the links between human cancers and specific environmental factors. The project is one of four winners of the Cancer Research United Kingdom Grand Challenge, announced February 10, 2017. This research examines human and animal cancers for unique patterns of genetic mutations that might result from chemical exposures. The characteristic patterns are called mutational fingerprints or mutational signatures. The samples are from carefully documented studies of rats and mice exposed to more than 100 chemical carcinogens. The study involved exposures of male and female rats and mice for 13-week and 2-year durations. The researchers will compare mutational fingerprints from the rodent tumors with those from human cancer tissues.

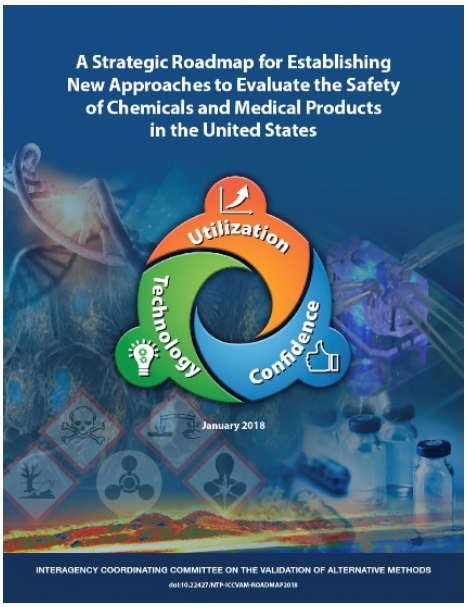
The study builds on initial evidence that certain environmental factors, such as ultraviolet radiation and tobacco, leave a distinct mutational fingerprint when they damage the DNA in human cells. At least 50 mutational fingerprints have been identified, but only about half have been linked to specific environmental factors.

The NTP Archives also is contributing to a project, "Identifying Preventable Causes of Cancer," led by Professor Sir Mike Stratton, M.D., Ph.D., and director of the Wellcome Trust Sanger Institute. Collaborators include scientists from the United States, United Kingdom, and France. Stratton presented the concept for the project in a January 12, 2017 lecture at NIEHS. Stratton's team plans to study mutational fingerprints from 5,000 pancreatic, kidney, esophageal, and colorectal cancer samples from around the world, comparing them with mutational fingerprints from samples in the NTP Archives and other data. This is the most comprehensive attempt ever made to compare animal and human cancer mutation signatures in relation to chemical exposures.

Arun Pandiri, Ph.D., head of the NTP Molecular Pathology Group at NIEHS, is coordinating the pathology evaluation and sample selection from the NTP Archives.

Ron Herbert, D.V.M., Ph.D., oversees the archives. The archives are an unmatched collection of publicly available research specimens, detailed documentation from chemical exposures, and pathology assessments, all of which make the NTP Archives especially useful for toxicological research.

# Public Forum on Alternatives to Animal Testing Highlights Next Steps

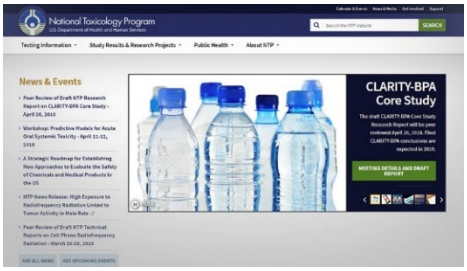



A plan for moving closer to the goal of replacing animals in U.S. safety testing and collaborations that have made possible the progress to date was highlighted at the May 23, 2017 public forum of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Many of the presentations at the annual public forum, held at NIH in Bethesda, Maryland, involved collaborations among federal agencies, between federal agencies and stakeholder groups, and among countries. Some of these efforts have already reduced the need to use animals for chemical safety testing. Other outcomes include technological advances that could improve hazard prediction and further reduce animal testing.

The forum was an opportunity for representatives from industry, animal welfare organizations, and other interested parties to discuss topics for inclusion in the Strategic Roadmap (to be published in 2018) on incorporating new approaches into safety testing of chemicals and medical products in the United States. The strategic roadmap document guides ICCVAM future activity.

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods organized the meeting on behalf of the ICCVAM and posted a video of the meeting and the presenters' slides on the NTP website.

# New NTP Website Getting Rave Reviews




Since March 2017, Beth Bowden, an information technology specialist in the NTP Program Operations Branch at NIEHS, has overseen the work of Signature Consulting Group, a contractor, to build a versatile, user-friendly new NTP website.

The NTP Information Technology Resources Advisory Committee, which includes members of the NIEHS Division of the NTP, has provided guidance and direction for each step in the website redesign process.

The new NTP website is current, visually appealing, and designed to engage both scientists and citizens. The site offers many new tools, including a feature—progressive disclosure—that facilitates navigation and improves usability. By displaying less clutter, the website allows users to focus on the main content of a page. Visitors can delve into the site's information without becoming lost. The site has been updated to be compatible with mobile technologies, favored by younger audiences.

In addition to providing easier navigation and a more appealing look, the redesign restructured the content to be more understandable. Headers and footers were improved to better tell NTP's story. The website includes some 11,000 pages, with information about meetings, articles, abstracts, and major NTP projects.

# At 10 Years, Tox21 Continues to Drive Toxicity Testing Forward

The Tox21 program has a 10-year track record of developing cutting-edge technology to better assess chemical toxicity in humans. In August 2017, the 10th World Congress on Alternatives and Animal Use dedicated a panel discussion to this milestone.

In his address to the World Congress meeting, Rick Paules, Ph.D., looked ahead to the next 5 years. Paules is the acting head of the NTP Biomolecular Screening Branch and serves as the NTP lead for the multiagency Tox21 program. Over the next 5 years, Tox21 scientists will concentrate on new and emerging alternatives, including computational models and 3D, organ-like model systems. Such alternatives could help address challenges for high-throughput screening, which include processing volatile chemicals and predicting dose-response relationships. Other priorities include incorporating individual variability, dose-response characteristics, and pharmacokinetics.

A new fact sheet captures milestones from the first decade of Tox21, including the more than 200 peer-reviewed articles published by the Tox21 researchers. Many of those papers shared results of robotic high-throughput screening assays of nearly 10,000 chemicals, performed at the National Center for Advancing Translational Science. These chemicals, referred to as the Tox21 library, are used in consumer products, industrial processes, agriculture, and drug development. Managing this library is a key Tox21 priority for the coming years.

Four federal agencies share the achievements of Tox21:

1. National Toxicology Program headquartered at NIEHS
2. Environmental Protection Agency
3. National Center for Advancing Translational Sciences
4. U.S. Food and Drug Administration

# NTP Public Health Impact on Regulatory Agencies

Federal and state regulatory agencies use NTP study data and recommendations in considering the need to regulate and test specific chemicals for the protection of human health. The NTP data and recommendations used by other agencies in FY 2017 are listed below. A full listing is available on the NTP website.

## Use of NTP Study Data or Recommendations by Federal and State Regulatory Agencies in FY 2017

| Notice | Summary of Notice | NTP Information Cited |
|---|---|---|
| Chemical Listed as Known to the State of California to Cause Cancer: Pentabromodiphenyl Ether Mixture [DE-71 (technical grade)]<br><br>[Effective Date: July 7, 2017] | The California Office of Environmental Health Hazard Assessment (OEHHA) added pentabromodiphenyl ether mixture [DE-71 (technical grade)] to the list of chemicals known to cause cancer under the “authoritative bodies” mechanism.<br><br>July 7, 2017 -- Proposition 65 | The listing of pentabromodiphenyl ether mixture [DE-71 (technical grade)] is based on formal ident(ification by the NTP, an authoritative body, that the chemical causes cancer. (see NTP Technical Report 589). |
| Notice of Amendment to Section 25705, No Significant Risk Level for Styrene<br><br>[Effective Date: July 1, 2017] | On May 4, 2017, the Office of Administrative Law approved the amendment of Title 27, California Code of Regulations, section 25705, No Significant Risk Level (NSRL) to establish a No Significant Risk Level of 27 micrograms per day for the chemical styrene.<br><br>May 11, 2017 -- Proposition 65 | NTP (2011). Report on Carcinogens, 12th Edition, U.S. Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina. NTP is designated an authoritative body for identifying chemicals that cause cancer. |
| Amendment to Section 25805, Maximum Allowable Dose Level (Oral) for Ethylene Glycol (Ingested)<br><br>[Effective Date: July 1, 2017] | On April 4, 2017, the Office of Administrative Law approved the amendment of Title 27, California Code of Regulations, section 25805, Maximum Allowable Dose Level (MADL) to establish a MADL of 8,700 (oral) micrograms per day for the chemical ethylene glycol (ingested).<br><br>April 6, 2017 -- Proposition 65 | NTP (2004). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol. NTP CERHR MON. 2004 Jan; (11):1-III36. PubMed PMID: 16015391. |
| Final Rule: Oxytetracycline; Pesticide Tolerances for Emergency Exemptions | This regulation establishes a time-limited tolerance for residues of oxytetracycline in or on fruit, citrus, or crop group 10-10. This action, in response to the Environmental Protection Agency’s (EPA’s) granting of an emergency exemption for the use of oxytetracycline in or on fruit, citrus, or crop group 10-10 under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorizing use of the pesticide in citrus production, established a time-limited maximum permissible level for residues of oxytetracycline in or on commodities in this crop group. The time-limited tolerance expires on December 31, 2019.<br><br>March 10, 2017 -- 82 FR 13245 | Based upon a literature search of toxicity in animals and the weight of the evidence as a whole, EPA has classified oxytetracycline as a “Group D” carcinogen (“Not Classifiable as to Human Carcinogenicity”). A review of the same animal toxicity data by the NTP Peer Review Committee was in agreement with this classification. Therefore, a dietary exposure assessment for the purpose of assessing cancer risk is unnecessary and was not conducted. (see NTP Technical Report 315). |

| Notice | Summary of Notice | NTP Information Cited |
|---|---|---|
| Final Rule: Formaldehyde Emission Standards for Composite Wood Products | EPA issued a final rule to implement the Formaldehyde Standards for Composite Wood Products Act, which added Title VI to the Toxic Substances Control Act (TSCA). The purpose of TSCA Title VI is to reduce formaldehyde emissions from composite wood products, which will reduce exposures to formaldehyde and result in benefits from avoided adverse health effects. This final rule also establishes a third-party certification program for hardwood plywood, medium-density fiberboard, and particleboard and includes procedures for the accreditation of third-party certifiers and general requirements for accreditation bodies and third-party certifiers.<br><br>December 12, 2016 -- 81 FR 89674 | NTP (2014). Report on Carcinogens, 13th Edition, U.S. Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina. NTP is designated an authoritative body for identifying chemicals that cause cancer. |
| Chemical Listed as Known to the State of California to Cause Cancer: Pentachlorophenol and By-Products of its Synthesis (Complex Mixture)<br><br>[Effective Date: October 21, 2016] | Effective October 21, 2016, OEHHA is adding pentachlorophenol and by-products of its synthesis (complex mixture) to the list of chemicals known to the state to cause cancer.<br><br>October 21, 2016 -- Proposition 65 | NTP (2014). Report on Carcinogens, 13th Edition, U.S. Department of Health and Human Services, Public Health Service, NTP, Research Triangle Park, North Carolina. NTP is designated an authoritative body for identifying chemicals that cause cancer. |

*CASRN = Chemical Abstracts Service Registry Number

# Additional Activities

During FY 2017, NTP participated in several meetings with stakeholders and the scientific community. At the 2017 annual meeting of the Society of Toxicology in Baltimore, Maryland, staff from NTP and NIEHS participated in numerous workshops, symposia, platform sessions, education and information sessions, and poster sessions. The full program, including all NTP and NIEHS activities, can be found at the Society of Toxicology website. NTP Director Linda Birnbaum received the Distinguished Toxicology Scholar award at the 2017 meeting.


Birnbaum said it was especially meaningful to accept the Distinguished Toxicology Scholar award because it represents recognition from her peers in toxicology.
(Photo courtesy of SOT)

NTP regularly hosts symposiums and workshops to discuss the state of the science or issues of public health concern. For example, NTP held “Pathology Potpourri,” an annual satellite symposium, in Montreal, Canada the day before the 2017 Society of Toxicologic Pathology meeting. The symposium’s goal is to present current diagnostic pathology or nomenclature issues to the toxicological pathology community. Proceedings will be published in the journal, “Toxicologic Pathology,” including summaries of presentations and images of specific pathologies that were used for audience voting and discussion on specific diagnostic and nomenclature issues.

NTP also hosted three workshop and webinar series in FY 2017 related to alternative methods development:

- BioMed21 – A Human Pathway-based Approach to Disease and Medicine.
- Using Informatics to Improve Data Analysis of Chemical Screening Assays Conducted in Zebrafish.
- Incorporating Chemical Information: Resources, Limitations, and Characterizing the Domain of Applicability for 21st Century Toxicity Testing.

# Publications

## NTP Reports and Documents

Morgan, DL, Dixon, D, King, DH, Travlos, GS, Herbert, RA, French, JE, Tokar, EJ, Waalkes, MP, Jokinen, MP. 2017. NTP Research Report on Absence of Formaldehyde-Induced Neoplasia in Trp53 Haploinsufficient Mice Exposed by Inhalation. NTP RR 3. Research Triangle Park, NC: National Toxicology Program. (3): 1-30. https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/rr03_508.pdf.

NTP Technical Report on the Toxicity Studies of o-Chloropyridine Administered Dermally and in Drinking Water to F344/N Rats and B6C3F1/N Mice. Research Triangle Park (NC): National Toxicology Program. Natl Toxicol Program Tox Rep Ser. 2017 Feb;(83):1-55; https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox83_508.pdf.

NTP Technical Report on the Toxicity Studies of Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) Administered by Gavage to F344/NTac Rats and B6C3F1/N Mice. Research Triangle Park (NC): National Toxicology Program. Natl Toxicol Program Tox Rep Ser. 2017 Aug;(85):1-43; https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox085_508.pdf.

NTP Technical Report on the Toxicology Studies of Indole-3-Carbinol in F344/N Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Indole-3-Carbinol in Harlan Sprague Dawley Rats and B6C3F1/N Mice (Gavage Studies). Research Triangle Park (NC): National Toxicology Program. Natl Toxicol Program Tox Rep Ser. 2017 Jul;(584):1-199; https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr584_508.pdf.

NTP Technical Report on the Toxicology and Carcinogenesis Studies of TRIM® VX in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N Mice (Inhalation Studies). Research Triangle Park (NC): National Toxicology Program. Natl Toxicol Program Tox Rep Ser. 2016 Nov;(591):1-186; https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr591_508.pdf.

## Journal Articles and Book Chapters

Research funding sources for each publication are indicated as follows:

[1] Funded by the NIEHS/NIOSH Interagency Agreement

[2] Funded by NIOSH voluntary allocations to the NTP

[3] Funded by the NIEHS/NCTR Interagency Agreement

[4] Funded by NCTR voluntary allocations to the NTP

[5] Funded by NIEHS voluntary allocations to the NTP

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# Learn About Us

## Mission and Goals

NTP was established in 1978 in response to concerns about potential human health effects of chemicals in our environment.

## Organizational Structure and Oversight

Three agencies form the core for NTP: NIOSH, NCTR, and NIEHS.

## Funding

The total NTP budget for FY 2017 and contracts that support NTP research.


## Program Contact Information

General inquiries, websites, and staff directory information.

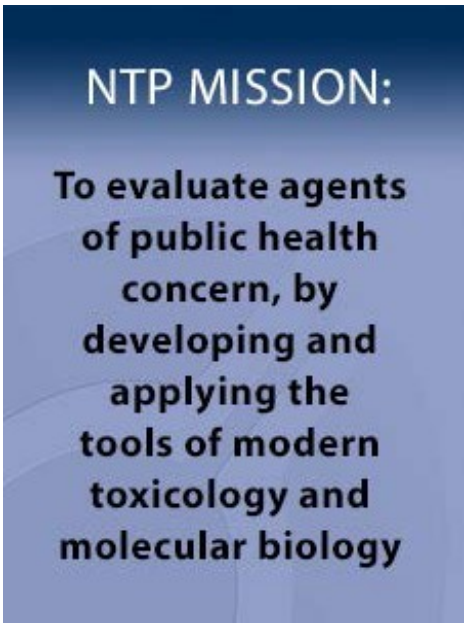
## Training Opportunities

NTP offers postdoctoral training fellowships designed to prepare trainees for careers in science.

## Interagency Agreements

In FY 2017, NIEHS provided support for NTP activities through interagency agreements with other federal agencies.

# Mission and Goals




The U.S. Department of Health, Education, and Welfare, now the U.S. Department of Health and Human Services, established NTP in 1978 in response to concerns about the potential human health effects of chemicals in our environment. NTP goals are to:

- Coordinate toxicology testing programs within the federal government.
- Strengthen the science base in toxicology.
- Develop and validate improved testing methods.
- Provide information about potentially toxic chemicals to health agencies, regulatory agencies, research agencies, scientific communities, medical communities, and the public.

NTP provides scientific data to regulatory agencies and other health-related research groups and interpretation and guidance in their appropriate use. The American people and government agencies, at state and federal levels, rely on NTP to provide a strong scientific basis for decisions aimed at protecting public health. In the past 39 years, NTP has studied and shared information on the health effects of more than 2,800 substances, including dietary supplements, industrial chemicals, consumer products, and complex mixtures.

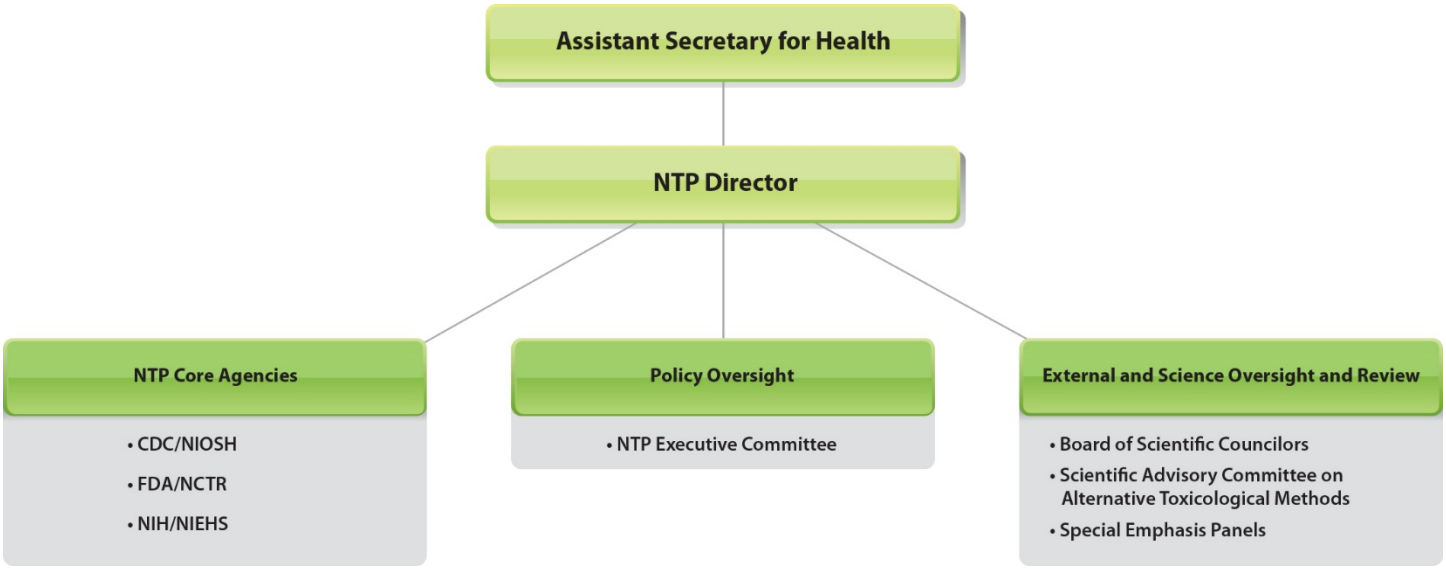
In following government-wide efforts to increase access to the results of federally funded scientific research, NTP maintains open communication and dialogue with the public, federal, and state agencies, industry, nongovernmental organizations, and academic institutions. The NTP website provides the public with a variety of information, including Federal Register notices, status of and data from NTP studies, access to NTP reports and journal publications, notifications through media releases, a calendar of upcoming events, and a newsletter, the NTP Update.

The public and other interested parties can stay abreast of NTP activities and events by subscribing to receive email of news. In addition, requests for information can be made through the Central Data Management office (984-287-3211or cdm@niehs.nih.gov), an online contact form, or the Freedom of Information Act coordinator.

NTP welcomes input on its programs and priorities. This input can be submitted in response to formal requests for public comment in Federal Register notices or informal submissions to the Office of Liaison, Policy, and Review (984-287-3209 or the online contact form).

# Organizational Structure and Oversight

Three agencies form the core for NTP: National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention; U.S. Food and Drug Administration, primarily through the National Center for Toxicological Research; and National Institute of Environmental Health Sciences of the National Institutes of Health.




NTP is located administratively at NIEHS, and Linda Birnbaum, Ph.D., is director of both NIEHS and NTP. In FY 2017, John Bucher, Ph.D., served as NTP associate director and director of the NTP Division at NIEHS, herein referred to as NIEHS/NTP, which is the focal point for NTP activities. NIEHS and NTP espouse best research practices and embrace developments in technology to discover how the environment affects people, maintaining leadership in the field of environmental health sciences by applying innovative research to address public health issues.

John Howard, M.D., is director of NIOSH. Staff from two NIOSH divisions participate in NTP activities. Elizabeth Whelan, Ph.D., chief of the Industrywide Studies Branch, and Cheryl Estill, Ph.D., supervisor of Industrial Hygiene, manage NTP activities within the Division of Surveillance, Hazard Evaluations, and Field Studies. Donald Beezhold, Ph.D., is the principal investigator for the "Immunotoxicity of Workplace Xenobiotics" project through an NCTR-NIEHS interagency agreement.

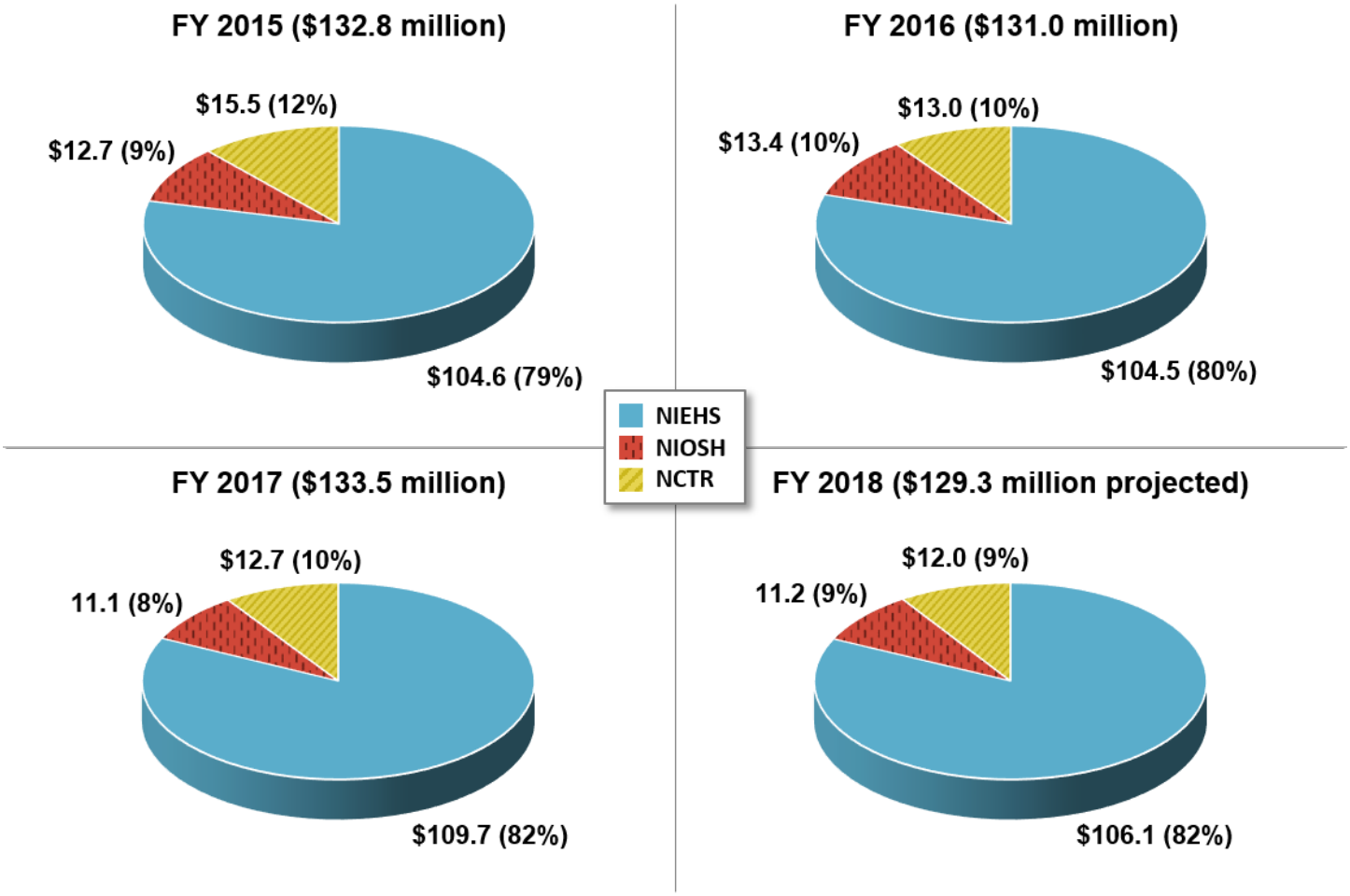
NIOSH's participation in NTP is consistent with its mandate to protect worker health and safety under the Occupational Safety and Health Act and the Federal Mine Safety and Health Act.

William Slikker Jr., Ph.D., (director of FDA/NCTR) and Goncalo Gamboa Da Costa, Ph.D., (project officer of the NCTR-NIEHS interagency agreement, Division of Biochemical Toxicology) provide management oversight and coordination of NTP activities within NCTR.

NCTR staff scientists partner with other researchers in FDA, other government agencies, academia, and industry to provide innovative technology, methods development, vital scientific training, and technical expertise. NCTR conducts an array of studies that reflect the NTP mission and are critical in supporting FDA product centers and their regulatory roles.

# Funding

NTP relies on voluntary allocations from the three core agencies—NIEHS, FDA/NCTR, and CDC/NIOSH—to support its activities. These allocations are specified after annual appropriations have been determined. The total NTP budget for FY 2017 was $133.5 million.




NTP conducts its research through in-house studies at the three core agencies or through contract laboratories or interagency agreements with other agencies. In FY 2017, NIEHS funded 39 contracts, listed below, held three workshops, three special emphasis panel peer-review meetings, and one scientific advisory meeting for NTP. CDC and FDA could have additional contracts that support some of their voluntary NTP efforts.

## NIEHS Contracts That Supported NTP Activities in FY 2017

| Description | Contractor |
|---|---|
| Analytical Chemistry Services | Battelle Memorial<br>Midwest Research Institute<br>Research Triangle Institute |
| Archives and Specimen Repository | Experimental Pathology Laboratories |
| Assessment of Exposure to Coal Tar Pitch Volatiles Containing PAHs in Coal Tar Sealant Applicators | Interagency Agreement (IAA) with NIOSH |

| Description | Contractor |
|---|---|
| Assessment of Occupational Exposure to Flame Retardants | IAA with NIOSH |
| Assessment of Occupationally Relevant Exposures | IAA with NIOSH |
| Bioinformatics Methylation Project | Laboratory Corp of America |
| Bioinformatics Support | SCIOME, LLC. |
| Collaborative Work with Ramazzini | DOE/ORISE |
| Conducting Comprehensive Toxicological Assessments | IAA with NCTR – FDA |
| Development of Tools for Evaluating NTP's Effectiveness | DOE Oakridge National Laboratory |
| Evaluation of Toxicity Following Early Life Exposure | Southern Research Institute |
| Evaluation of Alternative Toxicological Methods | Integrated Laboratory Systems |
| Evaluation of the Toxicity of Selected Chemicals | Battelle Memorial |
| Genetic Toxicity Testing Support Services | Integrated Laboratory Systems |
| Hepatocytes | Bioreclamation, LLC |
| Immunotoxicity | Burleson Research Technologies |
| Immunotoxicity of Workplace Xenobiotics | IAA with NIOSH |
| In-Life Data Collection and Management System | INSTEM, LSS |
| NTP Information Systems Support | Signature Consulting Group, LLC |
| NTP Statistical and Computer Support | SRA International |
| NTP Technical Reports Preparation Support Services | Biotechnical Sciences, Inc. |
| Pathology Support | Experimental Pathology Laboratories<br>Integrated Laboratory Systems<br>PAI/Charles River Laboratories |
| Production of B6C3F1 Mice | Taconic Biosciences, Inc. |
| Quality Assessment Support/Audits & Inspections | CSS-Dynamac Corporation |
| Reproductive Assessments by Continuous Breeding | Research Triangle Institute |
| Scientific Information Management and Literature-Based Evaluations for the NTP | ICF |
| Scientific Positions | Kelly Scientific |
| SECAS - Search for Environmental Contaminants Ancillary Study | IAA with CDC |
| Statistical Support | Social and Scientific Systems |

| Description | Contractor |
|---|---|
| Support for Toxicological Data | Vistronix, LLC |
| Toxicity Profiling Using HTS – TOX 21 | IAA with NHGRI/NCATS |
| Toxicological and Carcinogenic Potential of Chemicals | Battelle Memorial |

# Program Contact Information

**For general inquiries, contact:**

Central Data Management

P.O. Box 12233, MD K2-05

Research Triangle Park, NC 27709

984-287-3211

Email cdm@niehs.nih.gov or use our contact form.

A Staff Directory is available.

# Interagency Agreements

In FY 2017, NIEHS provided support for NTP activities through interagency agreements with other federal agencies.

## FDA/NCTR

Under an interagency agreement, NIEHS and FDA conduct toxicology studies on FDA-regulated agents nominated to NTP at the National Center for Toxicological Research. These studies are designed to provide FDA and other regulatory agencies with hazard identification and dose-response data to support risk assessment and risk management decisions that could affect public health. The interagency agreement supports studies on endocrine active agents, dietary supplements, food contaminants, AIDS therapeutics, pediatric medicines, electromagnetic radiation, cosmetics, and nanoscale materials. Studies in these areas have produced 18 published NTP Technical Reports and over 250 peer-reviewed journal publications. The studies have led to an increased understanding of the pharmacokinetics, mode of action, and dose-response relationships of the substances and to refinements of risk assessment models. Further information about NTP at the National Center for Toxicological Research and current research can be found in the Partner Agency Research section of this annual report.

## CDC/NIOSH

NIEHS/NTP has two interagency agreements with the National Institute for Occupational Safety and Health (NIOSH). Studies under the interagency agreement on “Immunotoxicity of Workplace Xenobiotics” assess the potential toxicity of exposures to substances such as fungi, mycotoxins, volatile organic compounds, lead, latex, nickel, isocyanates, nanomaterials, and beryllium in occupationally exposed populations such as miners, farmers, health care workers, autoworkers, and firefighters. A second interagency agreement between NIEHS and NIOSH supports development of methods to assess complex mixtures, such as asphalt fumes, welding fumes, and tungsten fibers, and to conduct occupational exposure assessments to identify toxicologically relevant exposures. Research under these agreements in FY 2017 evaluated occupational exposure to bisphenol A, alternative flame retardants, and polycyclic aromatic hydrocarbons in coal tar sealants. For more information, see the Partner Agency Research section of the Annual Report.

## NIH/NCATS/DPI

This interagency agreement supports ongoing and anticipated studies conducted at the National Center for Advancing Translational Sciences/Division of Pre-Clinical Innovation to evaluate high-throughput and high-content screening assays in support of Tox21. Tox21 is a collaboration among federal agencies to characterize the potential toxicity of chemicals by using cells and isolated molecular targets instead of laboratory animals. This interagency agreement between NIEHS/NTP and the division produces data for information-poor substances to help prioritize them for further studies, including toxicological evaluation, mechanisms of action investigation, and development of predictive modeling for biological response.

## Additional Agreements

NTP also established several smaller interagency agreements to conduct research, listed below.

## Additional Interagency Agreements in FY 2017

| Study—Agency | Description |
|---|---|
| Development of Tools for Evaluating NTP's Effectiveness—U.S. Department of Energy | Research and develop tools, such as publication mining tools, that NTP can use to evaluate the use and impact of its work across the agencies and stakeholders to whom the work is disseminated and extract and organize data (e.g., potential outcomes and impacts) from NTP's large inventory of documents (e.g., publications and progress reports). |
| Accelerating Development and Use of Computational Methods and Models—Environmental Protection Agency | Accelerate development and use of methods/models for quantitative and qualitative risk assessments of environmental chemicals. |

# Training Opportunities

NIEHS/NTP offers a limited number of postdoctoral training fellowships to prepare trainees for careers in pharmaceutical and chemical industries, regulatory agencies, and academia. In FY 2017, NIEHS/NTP staff mentored 15 postdoctoral fellows at NIEHS. Full details on opportunities, benefits, and the application process can be found on the NIEHS training website. The training program has six focal areas:

1. Applied toxicology and carcinogenesis
2. Biomolecular screening and computational toxicology
3. Health assessment and translation
4. Laboratory animal medicine
5. Systems and mechanistic toxicology
6. Toxicological pathology

## NIEHS/NTP Training Program Postdoctoral Fellows in FY 2017

| Training Program | Fellow |
|---|---|
| Applied toxicology and carcinogenesis | Natasha Catlin<br>Anika Dzierlenga<br>Kelly Shipkowski |
| Biomolecular screening and computational toxicology | Sreenivasa Ramaiahgari |
| Health assessment and translation | Katie Pelch |
| Laboratory animal medicine | Manushree Bharadwaj<br>David Crizer<br>Jingli Liu<br>Tony Luz |
| Systems and mechanistic toxicology | Sheba Churchill<br>Gopi Gadupudi<br>Miaofel Xu |
| Toxicological pathology | Daven Jackson-Humbles<br>Gregory Krane<br>Eui Jae Sung |

# Scientific and Public Input Opportunities

## Nominations

NTP nominations are open to the public, and continually accepted through the NTP website.

## NTP Board of Scientific Counselors

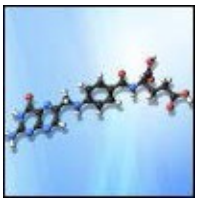
The NTP Board of Scientific Counselors (BSC) provides scientific oversight to NTP on the scientific merit of its programs and activities.

## SACATM

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) provides advice on priorities and activities related to alternative toxicological test methods.

## NTP Executive Committee

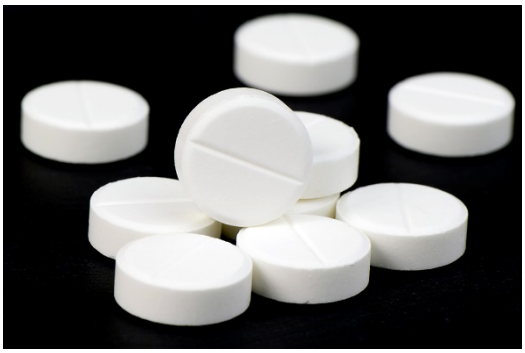
The NTP Executive Committee provides programmatic and policy oversight to the NTP director.



## Special Emphasis Panels

NTP uses ad hoc scientific panels to provide independent scientific peer review and advice on targeted issues including the review of NTP technical reports and monographs.

# Nominations



NTP continually accepts and reviews nominations for studies in its research and testing program. The NTP nomination process is open to the public, and nominations can be submitted through the NTP website. Agencies represented on the NTP Executive Committee also identify and forward nominations to NTP.

For new research projects or studies of substantial scope and complexity, NTP research concepts or project plans are prepared to facilitate external review as part of a multistep process with input from NTP participating federal agencies, the Board of Scientific Counselors, and the public. In addition to new research projects, NTP conducts targeted studies to extend or explain findings observed in previous studies and to address nominations closely aligned with current research efforts.

A 2016 nomination from the Environmental Working Group requested that NTP evaluate the hypothesis that mixtures of unrelated substances with specific reported biological activity corresponding to cancer “hallmarks” could jointly contribute to cancer development. Plans and progress toward addressing this nomination were presented at the NTP Board of Scientific Counselors meeting in June 2017.

New projects were initiated in FY 2017 to address nominations for adverse reproductive outcomes of certain analgesics and to explore the possibility of using Tox21 approaches to query biological activities of concern associated with exposure to consumer products intended for children.

Questions about the nomination, review, and selection process can be sent to Scott Masten, Ph.D.

## Research and Testing Projects Initiated in FY 2017

| Project & Study Scientist | Project Description |
|---|---|
| Reproductive Outcomes Following Developmental Exposure to Acetaminophen<br>Study Scientist: Vicki Sutherland | Recent studies suggest that maternal consumption of mild analgesics during pregnancy has detrimental effects on male reproductive tract development (e.g., cryptorchidism). This rat study evaluates reproductive and endocrine endpoints in offspring exposed to acetaminophen during the period of male androgen-dependent development. |
| Screening for Biological Activities of Concern in Consumer Products<br>Study Scientist: Scott Masten | Targeted screening approaches and methods are being explored to evaluate the bioactivity of physiologically relevant extracts of selected consumer products used by children. |
| Cancer Network and Environmental Exposure Research Agenda (CNVERGE)<br>Study Scientist: Cynthia Rider | CNVERGE applies a systems-based approach to use adverse outcome pathways as a framework for identifying environmental exposures that might converge at the pathway or tissue level to contribute cumulatively to disease development. |

# NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors, a federally chartered advisory group whose members are appointed by HHS, oversees the scientific merit of NTP programs and activities. The Board includes scientists, primarily from the public and private sectors, with expertise relevant to NTP activities. The Board's charter and current roster are available on the NTP webpage. In FY 2017, Mary Wolfe, Ph.D., served as the designated federal officer and manager of the Board. FY 2017 members are listed below.

The Board met twice in FY 2017: December 14–15, 2016 and June 29, 2017. In December, the Board heard reports by:

- Carl Cernigila, Ph.D., director of the FDA National Center for Toxicological Research Division of Microbiology, on center efforts to discover how exposures to hazardous chemicals affect the microbial ecosystem in the human gastrointestinal tract.
- Elizabeth Whelan, Ph.D., chief of the Industrywide Studies Branch of the Division of Surveillance, Hazard Evaluations, and Field Studies, on seven research projects led by the National Institute for Occupational Safety and Health in collaboration with NTP.
- Ruth Lunn, Ph.D., of NIEHS/NTP on the recently released 14th Report on Carcinogens.
- Warren Casey, Ph.D., on efforts by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods to spearhead development of a new framework for the safety testing of drugs and chemicals, which aims to provide more human-relevant toxicology data while reducing the use of animals.

The Board also discussed:

- An initiative to consider antimony trioxide for possible listing in the Report on Carcinogens.
- The peer-review of the "Draft NTP Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS)."

The second meeting focused on NTP's research investigating how exposures to multiple chemicals affect human health. Cynthia Rider, Ph.D., of NTP briefed the Board on the challenges of evaluating the toxicity of chemical mixtures and the substantial progress NTP has made in this area. Rider also briefed the Board on the NTP crumb rubber research program and discussed a potential project to examine chemical mixtures in children's products.

**NTP Board of Scientific Counselors members and NTP staff at the June 2017 BSC meeting**

## NTP Board of Scientific Counselors Membership Roster FY 2017

| Name and Title | Affiliation | Term End Date |
|---|---|---|
| Cynthia Afshari, Ph.D.<br>Scientific Executive Director | Amgen, Inc.<br>Thousand Oaks, California | 6/30/19 |
| Norman J. Barlow, D.V.M., Ph.D.<br>Vice President and Global Head | Johnson and Johnson<br>Spring House, Pennsylvania | 6/30/19 |
| Paul Brandt-Rauf, Dr.P.H., M.D., Sc.D.<br>Office of the Dean | Drexel University<br>Philadelphia, Pennsylvania | 6/30/20 |
| Myrtle Davis, D.V.M., Ph.D.<br>Executive Director, Discovery Toxicology, Pharmaceutical Candidate Optimization | Bristol-Myers Squibb<br>New York, New York | 6/30/20 |
| Mary Beth Genter, Ph.D.<br>Associate Professor, Department of Environmental Health | University of Cincinnati<br>Goshan, Ohio | 6/30/17 |
| Daniel Kass, M.S.P.H.<br>Executive Vice President, Environmental Health | Vital Strategies<br>New York, New York | 6/30/19 |
| Steven Markowitz, M.D., Dr.P.H.<br>Professor and Director, Center for the Biology of Natural Systems | Queens College<br>City University of New York<br>Flushing, New York | 6/30/17 |
| Kenneth McMartin, Ph.D.<br>Board Chair<br>Professor, Pharmacology, Toxicology, and Neuroscience | Louisiana State University Health Science Center<br>Shreveport, Louisiana | 6/30/19 |
| Kenneth Ramos, M.D., Ph.D.<br>Associate Vice President, Precision Health Sciences Center | Arizona Health Sciences Center<br>Tucson, Arizona | 6/30/19 |
| Jennifer Sass, Ph.D.<br>Senior Scientist | Natural Resources Defense Council<br>Washington, District of Columbia | 6/30/20 |
| James Stevens, Ph.D.<br>Distinguished Research Fellow | Lilly Research Laboratories<br>Indianapolis, Indiana | 6/30/19 |

| Name and Title | Affiliation | Term End Date |
|---|---|---|
| Donald G. Stump, Ph.D., D.A.B.T.<br>Vice President, Nonclinical Safety Science | WIL Research<br>Ashland, Ohio | 6/30/20 |
| Katrina Waters, Ph.D.<br>Deputy Director, Biological Sciences Division | Pacific Northwest National Laboratory<br>Richland, Washington | 6/30/19 |

# SACATM

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee established on January 9, 2002 in response to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Authorization Act of 2000 (42 U.S.C. 285l-3[d]). SACATM advises ICCVAM, the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and the director of NIEHS and NTP regarding statutorily mandated duties of ICCVAM and activities of NICEATM. SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. The SACATM charter and current roster are available on the NTP website, and the roster for FY 2017 is listed below. SACATM typically meets once a year and members serve rotating terms of up to 4 years. Mary Wolfe, Ph.D., served as the FY 2017 designated federal officer and manager of SACATM.

SACATM met on September 18–19, 2017, at the NIH Natcher Conference Center in Bethesda, Maryland. At the meeting, Warren Casey, Ph.D., director of NICEATM, updated SACATM on the efforts to construct a strategic roadmap that would guide development of new approaches for evaluating the safety of chemicals and medical products in the United States. SACATM members expressed a generally positive response to the roadmap and provided feedback on topics related to its implementation. The topics included encouraging federal agencies and regulated industries to adopt new toxicological methods, connecting users with new tools, and establishing greater confidence in new methods.

**Members of SACATM and ICCVAM and staff from NIEHS and NTP at the September 2016 SACATM meeting**

## SACATM Membership Roster FY 2017

| Name and Title | Affiliation | Term End Date |
|---|---|---|
| Brian Berridge, D.V.M., Ph.D., D.A.C.V.P.<br>Director, WW Animal Research Strategy | GlaxoSmithKline<br>King of Prussia, Pennsylvania | 12/31/17 |
| Michael B. Bolger, Ph.D.<br>Chief Scientist | Simulations Plus, Inc.<br>Lancaster, California | 11/30/20 |
| Kelly P. Coleman, Ph.D., D.A.B.T., R.A.C.<br>Distinguished Scientist and Technical Fellow | Medtronic PLC<br>Minneapolis, Minnesota | 11/30/20 |
| Hisham Hamadeh, Ph.D., D.A.B.T., M.B.A. Director, Comparative Biology and Safety Sciences | Amgen, Inc.<br>Thousand Oaks, California | 11/30/19 |
| William P. Janzen<br>Committee Chair<br>Executive Director of Lead Discovery | Epizyme, Inc.<br>Cambridge, Massachusetts | 11/20/18 |
| Safdar A. Khan, D.V.M., M.S., Ph.D., D.A.B.V.T.<br>Associate Director, Global Pharmacovigilance | Zoetis<br>Kalamazoo, Michigan | 11/30/16 |
| Lawrence Milchak, Ph.D., D.A.B.T.<br>Senior Manager, Toxicology and Strategic Services | 3M<br>St. Paul, Minnesota | 11/30/19 |
| Pamela J. Spencer, Ph.D., D.A.B.T.<br>Director of Regulatory and Product Stewardship | ANGUS Chemical Company<br>Buffalo Grove, Illinois | 11/30/19 |
| Catherine E. Willett, Ph.D.<br>Director, Regulatory Toxicology, Risk Assessment and Alternatives | The Humane Society of the United States<br>Gaithersburg, Maryland | 11/30/18 |
| ClarLynda Williams-Devane, Ph.D.<br>Director, Bioinformatics, Genomics, and Computational Chemistry<br>Biotechnology Biomedical Research Institute | North Carolina Central University<br>Durham, North Carolina | 11/30/20 |
| Wei Xu, Ph.D.<br>Associate Professor, Department of Oncology<br>McArdle Laboratory for Cancer Research | University of Wisconsin at Madison<br>Madison, Wisconsin | 11/30/18 |
| Hao Zhu, Ph.D.<br>Assistant Professor, Department of Chemistry | Rutgers University<br>Camden, New Jersey | 11/30/19 |

# NTP Executive Committee

The NTP Executive Committee provides programmatic and policy oversight support to the NTP director. The committee meets once or twice a year in a closed forum. Members include the heads, or their designees, from the following federal agencies.

- U.S. Consumer Product Safety Commission.
- U.S. Department of Defense.
- U.S. Environmental Protection Agency.
- U.S. Food and Drug Administration.
- National Cancer Institute.
- National Center for Environmental Health/Agency for Toxic Substances and Disease Registry.
- National Institute of Environmental Health Sciences.
- National Institute for Occupational Safety and Health.
- Occupational Safety and Health Administration.

To enhance agency interactions by streamlining communication, NTP uses agency points of contact, rather than formal committees. Agency points of contact have a dedicated responsibility and time commitment, are knowledgeable about the NTP mission and programs and their agency's resources, and bring the most relevant agency expertise to bear on NTP issues.

# Special Emphasis Panels

NTP uses ad hoc scientific panels, referred to as special emphasis panels, to provide independent scientific peer review and advice on targeted issues, such as agents of public health concern, new and revised toxicological test methods, and others. These panels help ensure that NTP receives transparent, unbiased, and scientifically rigorous input for its use in making credible decisions about human health hazards, setting research and testing priorities, and evaluating test methods for toxicity screening.

## NTP Technical Report Peer Review Panels

NTP Technical Reports are published results of long-term studies, generally 2-year rodent toxicology and carcinogenesis studies. NTP convenes external scientific panels to peer review draft technical reports at public meetings held at NIEHS. All reviews provide the opportunity for public comment. For each technical report, the panel is charged with reviewing the scientific and technical elements and presentation of the study and determining whether the study's experimental design and conduct support NTP conclusions regarding the carcinogenic activity of the substance tested. One technical report meeting was held in FY 2017, on July 13.

Three draft technical reports were peer reviewed at the July meeting: dietary zinc; 2,3 butanedione; and p-chloro-α,α,α-trifluorotoluene. The peer-review panel included individuals with expertise in molecular carcinogenesis, physiology, pharmacology, inhalation pathology, statistics, inhalation toxicology, genetic toxicology, occupational health, and general toxicology and pathology. Mary Wolfe, Ph.D., served as designated federal officer for the meeting. The panel agreed that elements and presentation of each study were appropriate and NTP's conclusions in the draft technical reports were sound. Additional information about this meeting can be found on the NTP Technical Reports Peer Review Panels webpage.

## Report on Carcinogens Peer Review Panels

NTP follows an established, four-part process in preparing the Report on Carcinogens. The Report monographs are prepared for each candidate substance selected for review and consist of a cancer evaluation component and a substance profile. NTP convenes external scientific panels to peer review draft Report monographs at meetings that are open to the public with time scheduled for oral public comment. The panels are charged with commenting on whether the draft cancer evaluation component is technically correct and clearly stated, whether NTP objectively presents and assesses the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria. For the draft substance profile, panels are charged with commenting on whether the scientific justification presented supports the preliminary NTP policy decision on the Report listing status.

On July 24, 2017, NTP convened a panel at NIEHS to peer review the draft Report monograph on haloacetic acids, which are found in the environment as byproducts of water disinfection. The panel was charged to:

1. Comment on whether the draft monograph was technically correct, clearly stated, and objectively presented.
2. Provide opinion on whether significant human exposure to haloacetic acids as water disinfection byproducts has been found.

The panel voted unanimously to accept NTP's conclusions on the draft level of evidence for carcinogenicity determination, based on the available scientific evidence in experimental animal and human cancer studies. They also agreed unanimously with NTP's preliminary listing recommendations in the Report. The review covered viral properties and human exposure, cancer studies in experimental animals, metabolism and mechanistic data, human cancer studies, an overall cancer evaluation, and the draft substance profile. Mary Wolfe, Ph.D., served as designated federal

officer for the peer-review meeting. After the meeting, the input from the panel was considered in finalizing the monograph. Additional information about this meeting can be found on the Peer Reviews of Report on Carcinogens Monographs webpage.

## NTP Expert Panels

NTP expert panels provide independent advice to NTP on agents of public health concern, new and revised toxicological test methods, or other topics. In August and September 2017, NTP hosted a series of four webinars to provide background information to an expert panel that is planned to convene in FY 2018 on the Draft NTP Approach to Genomic Dose-Response Modeling. The webinar speakers and subjects are listed below.

**Webinar 1: The NTP Proposed Approach to Genomic Dose-Response Modeling, August 30**

Scott Auerbach, Ph.D., of the National Toxicology Program presented the NTP proposed approach to genomic dose-response modeling. This approach is consistent with the modeling approach the EPA recommends for continuous non-genomic endpoints, which is implemented in its Benchmark Dose Software.

**Webinar 2: Overview of the U.S. Army Approach to Genomic Dose-Response Modeling, September 1**

Lyle Burgoon, Ph.D., U.S. Army Engineer Research and Development Center, discussed the Good Risk Assessment Value for Environmental Exposures approach. This approach is used in estimating points of departure from dose-response data.

**Webinar 3: Overview of the NC State Approach to Genomic Dose-Response Modeling, September 13**

Fred Wright, Ph.D., North Carolina State University, gave an overview of the NC State approach to handling genomic dose-response data for cell lines treated with chemicals at varying concentrations.

**Webinar 4: An Automated Method to Identify Dose-Responsive Genes and Quantitate Points of Departure (PODs) from Transcriptomic Data, September 25**

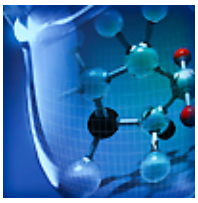
David Gerhold, Ph.D., National Center for Advancing Translational Sciences, presented an automated method to identify dose-responsive genes and quantitate points of departure from transcriptomic data.

Additional information about the webinar series is available online. General information about NTP expert panel meetings can be found on the NTP Expert Panels webpage.

# Research and Testing

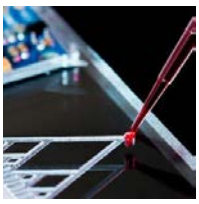
## Tox21

The Toxicology in the 21st Century (Tox21) program is a federal collaboration that uses automated high-throughput screening methods to quickly test chemicals across a battery of assays.



## Testing and Toxicology Studies

The NTP testing program evaluates substances for a variety of health-related effects, generally using rodent models for study.



## NICEATM

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), an office within NIEHS/NTP, supports the development and evaluation of new, revised, and alternative methods to identify potential hazards to human health and the environment, with a focus on replacing, reducing, or refining animal use.


## ICCVAM

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is a permanent interagency committee of NIEHS.

# Tox21

## About Tox21

The Toxicology in the 21st Century (Tox21) program is a federal collaboration that uses automated high-throughput screening methods to quickly test chemicals across a battery of assays.

## Tox21 Projects

A list of NTP Tox21 projects conducted in FY 2017.

# About Tox21

Toxicology in the 21st Century (Tox21) is a unique federal collaboration among the National Institutes of Health (NIH), including the National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS) and the National Center for Advancing Translational Sciences (NCATS), Environmental Protection Agency (EPA), and U.S. Food and Drug Administration (FDA). Its purpose is to develop new methods to rapidly test whether chemicals adversely affect human health. Tox21 uses robotic, high-throughput screening methods and other testing approaches to evaluate large numbers of chemicals quickly and efficiently to provide insight into potential human health effects. Bioinformatics and computational toxicology support for Tox21 is provided by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods.


## Related Links

Tox21 Projects in 2017

# Tox21 Projects

**Also see**:

Tox21 Background

NTP Tox21 projects in FY 2017 were carried out by the NIEHS/NTP staff listed below.

## Assay Development

| Project & Study Scientist | Project Summary |
|---|---|
| Development of a stable cell line to screen compounds that affect the estrogen-related receptor/peroxisome proliferator-activated receptor coactivator pathway<br><br>Study Scientists: Alex Merrick, Tina Teng | Development of an assay to detect compounds that interfere with the estrogen-related receptor/peroxisome proliferator-activated receptor gamma coactivator pathway, a critical pathway for metabolic homeostasis. Stable human cell lines expressing the appropriate reporter construct were successfully generated.<br><br>Quantitative high-throughput screening efforts with the Library of Pharmacologically Active Compounds (LOPAC) were completed and a manuscript is in press. Quantitative high-throughput screening of the 10K library was completed, in FY 2016, and two peer-reviewed manuscripts describing the results were published in FY 2017. |
| Use of HepaRG cells for high-content screening<br><br>Study Scientists: Stephen Ferguson, Sreenivasa Ramaiahgari | Establishment of metabolically functional human HepaRG liver cells (derived from a human hepatic progenitor cell line) in 96-well or 384-well format for completing multiplex, high-content screening assays in collaboration with the NCATS Chemical Genomics Center. Studies to characterize the metabolism of xenobiotic compounds in these cells began in FY 2016 and were published in FY 2017. |
| Testing of gene signatures and profiles in NTP archival tissues<br><br>Study Scientist: Alex Merrick | Determination of whether RNA extracted from fixed tissue block can be used to measure gene signatures and develop chemically induced transcriptiomic profiles. The goal is to measure molecular changes caused by chemical exposures in rat and mouse organs. An effort to establish a relational database to allow identification and linkage of all tissues in the NTP Archives is underway. The tissue blocks, stored at the NTP Archives, were derived from NTP studies. |
| Screening of chemical toxicity in stem cells<br><br>Study Scientists: Stephen Ferguson, Fred Parham, Jui-Hua Hsieh, Mamta Behl | Screening for chemical toxicity in human or mouse stem cell lines (undifferentiated or differentiated) by quantitative high-throughput screening at the NCATS Chemical Genomics Center or by using lower throughput assays at NIEHS. Stem cell technology platforms and model systems shown to be useful for in vitro toxicology screening were employed with larger sets of chemicals for hazard identification and chemical prioritization for toxicity testing. Data were generated on a library of 80+ predominantly developmental neurotoxicants evaluated for effects on neurite outgrowth in a human stem cell-derived neural cell population, cytotoxicity in different neural populations derived from human stem cells, and effects on the beating of human stem cell-derived cardiomyocytes. Dose-response analyses have been completed on the data from these assays. Two manuscripts were published in FY 2017. |

| | |
|---|---|
| High-throughput assays and computational models to replace current EPA Endocrine Disruptor Screening Program Tier 1 tests<br><br>Study Scientists: Warren Casey, Nicole Kleinstreuer | Development of an approach using validated ToxCast and Tox21 high-throughput assays and an associated computational model to replace three Tier 1 tests currently used to assess estrogenic activity in the EPA Endocrine Disruptor Screening Program. The approach was developed and validated by EPA and NICEATM scientists. EPA solicited public comments on the plan in June 2015. The method has been described in several publications. In FY 2017, a similar computational model was developed for androgenic activity. |

## Data Analysis

| Project & Study Scientist | Project Summary |
|---|---|
| Analysis of Tox21 quantitative high-throughput screening assay data<br><br>Study Scientist: Jui-Hua Hsieh | Development of data analysis pipelines for Tox21 Phase II quantitative high-throughput screening data to determine the activity of compounds in assays. The developed ranking, or calling procedure, accounts for compound potency, efficacy, and data reproducibility. A manuscript describing this pipeline was published, and computational tools to analyze Tox21 data have been made publicly available through the Tox21 Toolbox on the NTP public website. |
| Prioritization of Tox21 compounds for genotoxicity<br><br>Study Scientists: Jui-Hua Hsieh, Kristine Witt, Stephanie Smith-Roe | Development of a prioritization approach that includes compounds showing clear evidence of activity in the quantitative high-throughput screening genotoxic assays and compounds that are weakly active based on chemical structure-activity relationship analysis. A manuscript using this approach as part of the analysis of the Tox21 quantitative high-throughput screening p53 activation assay was published in FY 2017. In addition, a more extensive modeling exercise has been completed using data from all Tox21 quantitative high-throughput screening assays. A second manuscript describing the outcome of this modeling approach for identifying genotoxicants is in preparation. |
| Design of Tox21 data exploration graphical user interface<br><br>Study Scientist: Jui-Hua Hsieh | Development of two graphical user interfaces for viewing Tox21 data. One graphical user interface is used to explore the concentration-response data in a line chart, and the second is used to explore compound similarity relationships in terms of their chemical structures and activities in Tox21 quantitative high-throughput screening assays. Prototype graphical user interfaces were first developed during FY 2013 and made public in FY 2015. These computational tools to analyze Tox21 data have since been developed further and expanded and made publicly available through the Tox21 Toolbox on the NTP public website. |
| Unsupervised, data-driven analysis of Tox21 assay data project<br><br>Study Scientist: Scott Auerbach | Use of unsupervised data analysis methods (data organization based on patterns and performed by software) to identify chemicals that exhibit biological properties similar to those of well-characterized toxicants from the quantitative high-throughput screening assays used to screen the 10K library. The results are being used to help prioritize compounds for more extensive toxicological testing. Updated web interfaces for multiple integrated tools will be made public in FY 2018 along with supporting manuscripts. |
| High-throughput in vitro-in vivo extrapolation (IVIVE) using Tox21 data | Development and refinement of ways to extrapolate all Tox21 chemical-concentration effect data to estimated human equivalent exposure doses. This effort builds on previous efforts (outside of |

| | |
|---|---|
| Study Scientist: Nisha Sipes | NTP) using high-throughput toxicokinetics models and combines it with in silico-estimated parameters. The development of this method is described in a manuscript published in FY 2017, and a publicly available web application is available through the Tox21 Toolbox on the NTP public website. Refinement of the model is ongoing. |
| Cell-line selection for Tox21 Phase III<br>Study Scientist: Nisha Sipes | Development and use of a data-driven approach for choosing cells to maximize biological diversity. This project is an established Tox21 Cross-Partner Project. Gene expression data from existing resources such as transcriptomics databases are used, and in vitro chemical testing is anticipated. |
| Aggregated hit-call of Tox21 data<br>Study Scientist: Nisha Sipes | Comparison of Tox21 data analysis methods, identification of higher-confidence chemical-assay actives, and development of a website for public access to the data and visualizations. A web interface with the aggregated hit-call function is anticipated in FY 2018. |
| Next-generation sequencing in toxicology<br>Study Scientists: Alex Merrick, Kristine Witt | Development of bioinformatics pipelines for genomic and transcriptomic gene expression and mutational analysis on a genome-wide level using next-generation sequencing technologies to build signatures of toxicity and chemical exposure. This effort was recently expanded to evaluate gene expression changes in frozen tissue samples obtained from genetic toxicity studies conducted at the NTP Genetic Toxicity Testing laboratory. In addition, new informatic tools have been developed to better identify long non-coding RNAs (lncRNAs). |
| Development of a reference database for estrogenic activity<br>Study Scientists: Warren Casey, Nicole Kleinstreuer | Support for future validation of high-throughput in vitro test methods and in silico models of estrogenic activity. NICEATM created a comprehensive database of high-quality in vivo data from over 1,000 scientific articles describing uterotrophic assay experiments for more than 2,660 distinct combinations of chemicals, studies, and protocols. These data have potential utility for developing adverse outcome pathways or models of estrogenic activity, prioritizing chemicals for further testing, or evaluating species-specific responses to chemicals. The database is described in a manuscript published in FY 2016. This activity is complete, but the database is being used as a training set for the automation of systematic reviews. |
| Development of an approach for in vitro-in vivo extrapolation using Tox21 data<br>Study Scientists: Warren Casey, Nicole Kleinstreuer | Quantitative correlation of in vitro and in vivo dosimetry for estrogen receptor reference chemicals. Using collective results of 16 Tox21 and ToxCast estrogen receptor pathway related assays, NICEATM developed and applied one-compartment or physiologically based pharmacokinetic models to correlate in vitro and in vivo dosimetry quantitatively for estrogen receptor reference chemicals. This approach highlights the importance of pharmacokinetic considerations in assessing and ranking endocrine-active chemicals based on in vitro, high-throughput screening assays. The initial approach and results are described in a published manuscript. Refinements to the approach are ongoing and are described in a manuscript expected to be published in FY 2018. |
| Evaluation of Tox21 data for predicting acute oral toxicity | Determination of the potential of high-throughput screening data to reduce animal use for acute oral toxicity testing. NICEATM analyzed high-throughput screening data from Tox21 and ToxCast for correlation and model fitting to rat oral LD50 data. The goal of |

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|---|---|
| Study Scientists: Warren Casey, Nicole Kleinstreuer | the analysis is to determine which tests or combinations of tests best characterize the rat oral toxicity data. The analysis suggests that combinations of in vitro assays and data from small model organisms, such as zebrafish, offer promise for predicting outcomes of rat acute oral toxicity tests. A global collaboration to use quantitative structure-activity relationships, Tox21, and other alternative sources to predict acute oral toxicity has been initiated. |
| Development of in silico methods for predicting metabolism<br><br>Study Scientist: Stephen Ferguson | Evaluation of various in silico methods for predicting the extent of xenobiotic metabolism and identifying metabolites and for prioritizing chemicals in the Tox21 10K library. Computational methods are used to partition the 10K library and develop subsets of chemicals that are likely to be metabolized appreciably in humans. |
| Selection of a target set of genes for use in a high-throughput transcriptomics screen<br><br>Study Scientists: Rick Paules, Scott Auerbach, Elizabeth Maull, Alex Merrick, Nisha Sipes | Identification of patterns of exposure-induced biological responses to characterize toxicity and disease pathways and facilitate extrapolation of findings from model species to humans. An effort has begun to select a set of 1,500 sentinel genes, or the S1500 set of genes, that best captures and represents the full biological response to exposures and disease for use in a high-throughput transcriptomics screening assay. Additional genes, identified as being particularly informative to toxicological processes, were added to the S1500 set, giving rise to the S1500+ set of approximately 2,750 genes. Criteria were developed for selecting the best target set of genes representing humans, rats, mice, and zebrafish. A manuscript describing this selection process was submitted in FY 2017 and is currently under revision. |
| Development of a computational model for androgen receptor pathway activity<br><br>Study Scientists: Warren Casey, Nicole Kleinstreuer | Integration of data from nine Tox21 and ToxCast assays into a computational model that predicts agonist and antagonist activity against the androgen receptor pathway. A manuscript describing this work was published in FY 2017. |
| Development of quantitative structure-activity relationship (QSAR) models to predict androgen receptor binding and activity<br><br>Study Scientists: Warren Casey, Nicole Kleinstreuer | Development of QSAR models to predict androgen receptor binding and activity. Using the computational model of the androgen receptor pathway, NICEATM developed QSAR models to predict androgen receptor binding and activity. These QSAR models are currently being refined, with a goal of using them to predict androgen receptor pathway activity of chemicals in the EPA Endocrine Disruptor Screening Program. A manuscript is expected to be published in FY 2018. |
| Development of a reference database for androgen receptor activity<br><br>Study Scientists: Warren Casey, Nicole Kleinstreuer | Development of a reference chemical list for in vitro androgen receptor binding and transactivation assay activity. NICEATM is conducting literature reviews to identify information about in vitro androgen receptor binding and transactivation assays for 127 putative androgen-active or androgen-inactive chemicals. The final database will be made available to the public on the NTP website. A parallel EPA data curation effort focuses on in vivo androgen activity data. These data will be used for evaluating high-throughput screening approaches, testing strategies, and further development of alternative test methods. A manuscript describing this work was published in FY 2017. |
| Development of a bioactivity-based, read-across approach | Use of bioactivity data from ToxCast to characterize untested environmental chemicals based on their similarities to chemicals with known toxicological effects. NICEATM used computational |

| | |
|---|---|
| Study Scientists: Warren Casey, Nicole Kleinstreuer | methods to create clusters of tested chemicals based on their activity in ToxCast assays. Clusters containing known toxicants were examined to identify similar in vitro bioactivity patterns in environmental chemicals lacking in vivo data. A new ICCVAM working group on the read-across approach was formed in FY 2017. |
| Development of software and methods for performing genomic dose-response analysis<br>Study Scientist: Scott Auerbach | Development of methods and software for performing genomic dose-response analysis to identify sensitive, screening-level potency estimates. An expert panel meeting to discuss the proposed method was held and software released in FY 2017. |

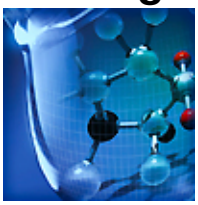
## Testing Projects

| Project & Study Scientist | Project Summary |
|---|---|
| Epigenetic changes in chemical toxicity<br>Study Scientist: Alex Merrick | Determination of methylation patterns on a genome-wide basis and validate selected CpG sites (regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide) altered by chemical exposure. Methylation of CpG sites can turn a gene off, while demethylation can cause transcriptional activation. A generalized approach for methylated DNA enrichment has been developed, and a manuscript describing the findings was submitted for publication. |
| Polycyclic aromatic hydrocarbons (PAHs)<br>Study Scientist: Stephen Ferguson | Evaluation of approximately 20 PAHs considered relevant to human exposure in metabolism-competent HepaRG cells using multiplexed high-content screening assays and gene expression platforms. Studies are in progress. |

## NTP WormTox Laboratory Projects

| Project & Study Scientist | Project Summary |
|---|---|
| Mitochondrial toxicants<br>Study Scientists: Windy Boyd, Mamta Behl, Jui-Hua Hsieh | Determination of the effects of the mitochondrial toxicant subset from the Tox21 10K library on *Caenorhabditis elegans* growth and in vivo adenosine-5'-triphosphate levels and membrane potential. Compounds for testing were received in late FY 2014. Testing occurred in FY 2015, and a manuscript reporting the findings was published in FY 2017. |

# Testing and Toxicology Studies



## About Testing and Toxicology Studies

The NTP testing program evaluates substances for a variety of health-related effects, generally using rodent models for study.

## Disposition, Metabolism, and Toxicokinetic Studies

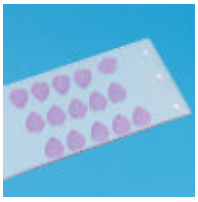
A list of substances evaluated through disposition, metabolism, and toxicokinetic studies.

## Genetic Toxicity Studies

A list of substances tested for genetic toxicity.

## Organ System Toxicity Studies

A list of substances tested for toxicity in organ systems.

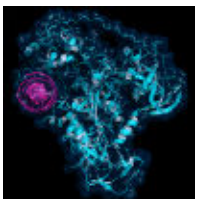


## Modified One-Generation Reproduction Studies

A list of planned or ongoing modified one-generation studies in FY 2017.

## Toxicology and Carcinogenicity Studies

A list of prechronic and chronic toxicity and carcinogenicity studies that were initiated, ongoing, or completed during FY 2017.



## Toxicogenomic Studies

A list of planned or ongoing toxicogenomic studies in FY 2017.

## Project Review Committee Approved

A list of studies approved by either the internal NIEHS/NTP protocol approval committee or the internal NIEHS/NTP project review committee that were not started during FY 2017.

# About Testing and Toxicology Studies

The NTP testing program evaluates substances for a variety of health-related effects, generally using rodent models. For each test article, a study team develops an appropriate testing strategy to address the identified research needs, and a project review committee evaluates the strategy. Reports and summaries of NTP toxicity studies, including carcinogenicity and effects on development and reproduction, are available on the NTP website.

The following Division of NTP branches at NIEHS are involved in the testing program: Biomolecular Screening Branch, led by acting chief Rick Paules, Ph.D.; Cellular and Molecular Pathology Branch, led by Robert Sills, D.V.M., Ph.D.; NTP Laboratory, led by acting chief Michael DeVito, Ph.D.; Program Operations Branch, led by Michelle Hooth, Ph.D.; and Toxicology Branch, led by Paul Foster, Ph.D.

Studies initiated, ongoing, or completed in 2017 are listed in this section.

## Related Links

Disposition, Metabolism, and Toxicokinetic Studies

Genetic Toxicity Studies

Organ System Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Project Review Committee Approved

## Disposition, Metabolism, and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its absorption, distribution, metabolism, and excretion in the body of both humans and test animals at differing levels of exposure, of all ages, via several routes of exposure, and under varying genetic backgrounds. Substances evaluated during FY 2017 are listed below.

**Disposition, Metabolism, and Toxicokinetics Studies During FY 2017**

| Test Article | CASRN* | Species | Route | Status | Study Scientist |
|---|---|---|---|---|---|
| 2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine | 95737-68-1 | Rabbit | Gavage | Initiated | Vicki Sutherland |
| 2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine | 95737-68-1 | Rats | Gavage | Initiated | Vicki Sutherland |
| 2-Ethylhexyl p-Methoxycinnamate | 5466-77-3 | Mice, Rats | Dermal, Gavage, Intravenous | Completed | Barry McIntyre |
| 2-Ethylhexyl p-Methoxycinnamate | 5466-77-3 | Rats | Dosed-Feed, Gavage, Intravenous | Ongoing | Barry McIntyre |
| Bisphenol AF | 1478-61-1 | Mice, Rats | Gavage, Intravenous | Ongoing | Vicki Sutherland |
| Bisphenol S | 80-09-1 | Mice, Rats | Gavage, Intravenous | Completed | Vicki Sutherland |
| Efavirenz (EFV) | 154598-52-4 | Mice | Gavage | Ongoing | Barry McIntyre |
| Emtricitabine (FTC) | 143491-57-0 | Mice | Gavage | Ongoing | Barry McIntyre |
| Hydroquinone | 123-31-9 | Mice, Rats | Gavage, Intravenous, Topical Application | Completed | Vicki Sutherland |
| Nanoscale Silver | 7440-22-4 | Rats | Gavage | Ongoing | Nigel Walker |
| Nanoscale Silver | 7440-22-4 | Rats | Intravenous | Ongoing | Nigel Walker |
| N-Butylbenzenesulfonamide | 3622-84-2 | Mice, Rats | Gavage, Intravenous | Completed | Cynthia Rider |
| Resveratrol | 501-36-0 | Mice, Rats | Gavage, Intravenous | Ongoing | Dori Germolec |
| Sodium arsenite | 7784-46-5 | Mice, Monkey, Rats | Dosed-Feed, Dosed-Water, Gavage | Ongoing | Daniel Doerge |
| Sulfolane | 126-33-0 | Mice, Rats | Gavage, Intravenous | Completed | Chad Blystone |
| Tenofovir Disoproxil Fumarate (TDF) | 202138-50-9 | Mice | Gavage | Ongoing | Barry McIntyre |
| Triclocarban | 101-20-2 | Mice, Rats | Dermal, Gavage | Completed | Vicki Sutherland |
| Triclosan | 3380-34-5 | Mice | Topical Application | Ongoing | Vicki Sutherland |
| Triclosan | 3380-34-5 | Mice | Topical Application | Ongoing | Jia-Long Fang |

| Test Article | CASRN* | Species | Route | Status | Study Scientist |
|---|---|---|---|---|---|
| Tris(4-chlorophenyl)methane | 27575-78-6 | Mice, Rats | Gavage, Intravenous | Completed | Natasha Catlin |
| Tris(4-chlorophenyl)methanol | 3010-80-8 | Mice, Rats | Gavage, Intravenous | Completed | Natasha Catlin |
| Tris(Chloropropyl)phosphate | 13674-84-5 | Mice, Rats | Gavage, Intravenous | Ongoing | Kristen Ryan |
| Vinpocetine | 42971-09-5 | Rats | Gavage | Ongoing | Natasha Catlin |

**Related Links:**

Genetic Toxicity Studies

Organ System Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Project Review Committee Approved

# Genetic Toxicity Studies

Genetic toxicity test results are used to help interpret general toxicity, carcinogenicity, or other in vivo test results and to provide a database for use in structure-activity relationship analysis. During FY 2017, NTP completed genetic toxicity testing for one substance, 2,2'-Dimorpholinodiethyl Ether (CASRN 6425-39-4).

**Related Links:**

Disposition, Metabolism, and Toxicokinetic Studies

Organ System Toxicity

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Project Review Committee Approved

## Organ System Toxicity Studies

NTP studies toxicity of environmental substances on development, reproduction, and on the nervous and immune systems. Organ systems toxicity studies conducted during FY 2017 are listed below.

**Neurotoxicity, Developmental Toxicity, and Reproductive Toxicity Studies During FY 2017**

| Test Article | CASRN* | Species | Testing Battery | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|---|
| 2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine | 95737-68-1 | Rabbit | Conventional Teratology | 3 weeks | Gavage | Scheduled | Vicki Sutherland |
| 2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine | 95737-68-1 | Rabbit | Conventional Teratology | GD 7-28 | Gavage | Initiated | Vicki Sutherland |
| 2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine | 95737-68-1 | Rabbit | Teratology Pilot Studies | -- | Gavage | Scheduled | Vicki Sutherland |
| 2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine | 95737-68-1 | Rats | Conventional Teratology | GD 6-21 | Gavage | Initiated | Vicki Sutherland |
| 2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine | 95737-68-1 | Rats | Immunotoxicity | 28 days | Gavage | Initiated | Vicki Sutherland |
| 2-Hydroxy-4-methoxybenzophenone | 131-57-7 | Rats | Developmental Toxicity | 35 days | Dosed-Feed | Completed | Deborah Hansen |
| 2-Hydroxy-4-methoxybenzophenone | 131-57-7 | Rats | Developmental Toxicity | GD 6 to PND 21 | Dosed-Feed | Ongoing | Deborah Hansen |
| 2-Hydroxy-4-methoxybenzophenone | 131-57-7 | Rats | Developmental Toxicity | GD 6 to GD 15 | Dosed-Feed | Ongoing | Deborah Hansen |
| Acenaphthenequinone | 82-86-0 | Mice | Immunotoxicity | 28 days | Gavage | Initiated | Cynthia Rider |
| Arsenic | 7440-38-2 | Rats | Developmental Toxicity | Pregnant dams through PND21 | Gavage & Dosed-Water | Initiated | Sherry Ferguson |
| Benz(j)aceanthrylene | 202-33-5 | Mice | Immunotoxicity | 28 days | Gavage | Scheduled | Cynthia Rider |
| Benzo(a)pyrene | 50-32-8 | Mice | Immunotoxicity | 28 days | Gavage | Ongoing | Cynthia Rider |
| Benzo(b)fluoranthene | 205-99-2 | Mice | Immunotoxicity | 28 days | Gavage | Scheduled | Dori Germolec |
| Benzo(c)fluorene | 205-12-9 | Mice | Immunotoxicity | 28 days | Gavage | Scheduled | Dori Germolec |

| Test Article | CASRN* | Species | Testing Battery | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|---|
| Benzo(k)fluoranthene | 207-08-9 | Mice | Immunotoxicity | 28 days | Gavage | Scheduled | Dori Germolec |
| Bisphenol AF | 1478-61-1 | Rats | Immunotoxicity | GD 6 - PND 96 | Dosed-Feed | Ongoing | Vicki Sutherland |
| Chrysene | 218-01-9 | Mice | Immunotoxicity | 28 days | Gavage | Initiated | Cynthia Rider |
| Dibenz(a,h)anthracene | 53-70-3 | Mice | Immunotoxicity | 28 days | Gavage | Initiated | Cynthia Rider |
| Dibenz(a,h)anthracene | 53-70-3 | Mice | Immunotoxicity | 8 GD - PND 42 | Subcutaneous Injection | Ongoing | Cynthia Rider |
| Dibenzo(a,l)pyrene | 191-30-0 | Mice | Immunotoxicity | 28 days | Gavage | Initiated | Cynthia Rider |
| Dibenzothiophene | 132-65-0 | Mice | Immunotoxicity | 28 days | Gavage | Initiated | Cynthia Rider |
| Efavirenz (EFV) | 154598-52-4 | Mice | Teratology Pilot Studies | GD 5 - PND 21 | Gavage | Ongoing | Anika Anika Dzierlenga |
| Indeno(1,2,3-cd)pyrene | 193-39-5 | Mice | Immunotoxicity | 28 days | Gavage | Scheduled | Cynthia Rider |
| N-Butylbenzenesulfonamide | 3622-84-2 | Mice | Immunotoxicity | 28 days | Dosed-Feed | Initiated | Cynthia Rider |
| N-Butylbenzenesulfonamide | 3622-84-2 | Rats | Immunotoxicity | GD 6 - PND 42 | Dosed-Feed | Initiated | Cynthia Rider |
| Phenanthrene | 85-01-8 | Mice | Immunotoxicity | 28 days | Gavage | Ongoing | Cynthia Rider |
| Pyrene | 129-00-0 | Mice | Immunotoxicity | 28 days | Gavage | Ongoing | Cynthia Rider |
| Sodium Metavanadate | 13718-26-8 | Mice | Immunotoxicity | 28 days | Dosed-Water | Ongoing | Georgia Roberts |
| Sulfolane | 126-33-0 | Mice | Immunotoxicity | 13 weeks | Gavage | Ongoing | Chad Blystone |
| Sulfolane | 126-33-0 | Rats | Immunotoxicity | 13 weeks | Gavage | Ongoing | Chad Blystone |
| Tenofovir Disoproxil Fumarate (TDF) | 202138-50-9 | Mice | Teratology Pilot Studies | GD 5 - PND 21 | Gavage | Ongoing | Anika Dzierlenga |

| Test Article | CASRN* | Species | Testing Battery | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|---|
| Tricombination FTC:TDF:EFV (1:1.5:3) | N/A | Mice | Maternal Transfer | GD 5-15 | Gavage | Completed | Barry McIntyre |
| Tricombination FTC:TDF:EFV (1:1.5:3) | N/A | Mice | Teratology Pilot Studies | GD 5 - GD 18 | Gavage | Completed | Barry McIntyre |
| Tricombination FTC:TDF:EFV (1:1.5:3) | N/A | Mice | Teratology Pilot Studies | -- | Gavage | Scheduled | Anika Dzierlenga |
| Tris(Chloropropyl)phosphate | 13674-84-5 | Rats | Immunotoxicity | GD 6 - PND 127 | Dosed-Feed | Initiated | Kristen Ryan |

**Related Links:**

Disposition, Metabolism, and Toxicokinetic Studies

Genetic Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Project Review Committee Approved

# Modified One-Generation Reproduction Studies

NTP modified one-generation study design emphasizes a full evaluation of the first generation offspring of animals and uses fewer animals than the classical multigenerational study design. These studies generate information on the effects of substances on prenatal development, postnatal development, and reproduction. Planned or ongoing modified one-generation studies are listed below.

### Modified One-Generation Studies in FY 2017

| Test Article | CASRN* | Species | Testing Battery | Status | Study Scientist |
|---|---|---|---|---|---|
| 2,2'-Dimorpholinodiethyl Ether | 6425-39-4 | Rats | Repeated Dose | Gavage | Georgia Roberts |
| Bisphenol S | 80-09-1 | Rats | Dose Range Finding | Dosed-Feed | Vicki Sutherland |
| Echinacea purpurea root extract | 90028-20-9 | Rats | Dose Range Finding | Gavage | Kristen Ryan |
| Ethylene glycol 2-ethylhexyl ether | 1559-35-9 | Rats | Dose Range Finding | Gavage | Chad Blystone |
| Isopropylated Phenol Phosphate | 68937-41-7 | Rats | Dose Range Finding | Dosed-Feed | Mamta Behl |
| N-Butylbenzenesulfonamide | 3622-84-2 | Rats | Developmental Toxicity | Dosed-Feed | Cynthia Rider |
| N-Butylbenzenesulfonamide | 3622-84-2 | Rats | F0 Generation | Dosed-Feed | Cynthia Rider |
| N-Butylbenzenesulfonamide | 3622-84-2 | Rats | Maternal Transfer | Dosed-Feed | Cynthia Rider |
| Resveratrol | 501-36-0 | Rats | F0 Generation | Gavage | Anika Dzierlenga |
| Simvastatin | 79902-63-9 | Rats | Dose Range Finding | Gavage | Barry McIntyre |
| Triclosan | 3380-34-5 | Rats | Dose Range Finding | Gavage | Vicki Sutherland |
| Tricombination FTC:TDF:EFV (1:1.5:3) | N/A | Mice | F0 Generation | Gavage | Anika Dzierlenga |
| Triphenyl Phosphate | 115-86-6 | Rats | Dose Range Finding | Dosed-Feed | Mamta Behl |
| Tris(4-chlorophenyl)methane | 27575-78-6 | Rats | Dose Range Finding | Dosed-Feed | Natasha Catlin |
| Valerian (Valeriana officinalis L.) root extract | 8057-49-6 | Rats | Dose Range Finding | Gavage | Georgia Roberts |
| Wyeth 14,643 (WY) | 50892-23-4 | Mice, Rats | Dose Range Finding | Gavage | Chad Blystone |

**Related Links:**

Disposition, Metabolism, and Toxicokinetic Studies

Genetic Toxicity Studies

Organ System Toxicity Studies

Toxicology and Carcinogenicity Studies

Toxicogenomic Studies

Project Review Committee Approved

## Toxicology and Carcinogenicity Studies

NTP performs toxicity studies to provide dose-setting information for chronic studies and to address specific deficiencies in the toxicology database for the chemical. Toxicology and carcinogenicity studies fall into two categories: prechronic toxicity studies and chronic two-year toxicology and carcinogenicity studies. Studies are generally conducted in rats and mice.

Each study type is performed according to the Specifications for the Conduct of Studies to Evaluate the Reproductive and Developmental Toxicity of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP) (May 2011). Prechronic and chronic toxicity studies and carcinogenicity studies, that were initiated, ongoing, or completed during FY 2017, are listed below.

**Prechronic Toxicology and Carcinogenicity Studies FY 2017**

| Test Article | CASRN* | Species | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|
| (+)-Usnic Acid | 7562-61-0 | Mice, Rats | 2 weeks | Dosed-Feed | Ongoing | Julian Leakey |
| (+)-Usnic Acid | 7562-61-0 | Mice, Rats | 90 days | Dosed-Feed | Ongoing | Julian Leakey |
| 1,2,4-trimethylbenzene | 95-63-6 | Mice, Rats | 13 weeks | Inhalation | Initiated | Dan Morgan |
| 1,2-Bis(2,4,6-tribromophenoxy)ethane | 37853-59-1 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| 1,2-bis(pentabromophenyl)ethane | 84852-53-9 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| 1,3,5,7,9,11-Hexabromocyclododecane | 25637-99-4 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| 1020 Long Multiwalled Carbon Nanotube | N/A | Mice, Rats | 2 years | Inhalation | Ongoing | Dan Morgan |
| 1020 Long Multiwalled Carbon Nanotube | N/A | Mice, Rats | 30 days | Inhalation | Ongoing | Dan Morgan |
| 2,2',4,4'-Tetrabromodiphenyl Ether | 5436-43-1 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| 2,2'-Dimorpholinodiethyl Ether | 6425-39-4 | Mice | 28 days | Gavage | Ongoing | Troy Hubbard |
| 2-Ethylhexyl Diphenyl Phosphate | 1241-94-7 | Rats | 5 days | Gavage | Ongoing | Scott Auerbach |
| 2-ethylhexyl-2,3,4,5-tetrabromobenzoate | 183658-27-7 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| 3,3',4,4'-Tetrachloroazobenzene | 14047-09-7 | Rats | 5 days | Gavage | Initiated | Mamta Behl |
| Acrylamide | 79-06-1 | Rats | 5 days | Gavage | Initiated | Frederick Beland |

| Test Article | CASRN* | Species | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|
| Aging Cohort Study: 12951/SvlmJ mouse | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aging Cohort Study: A/J mouse | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aging Cohort Study: B6C3F1J mouse | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aging Cohort Study: C3H/HeJ mouse | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aging Cohort Study: C57/BL/6J mouse | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aging Cohort Study: CAST/EiJ mouse | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aging Cohort Study: NOD. B10Sn-H2(b)/J | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aging Cohort Study: NZO/HiLtJ mouse | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aging Cohort Study: PWK/PhJ mouse | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aging Cohort Study: WSB/EIJ mouse | N/A | Mice | 2 years | N/A | Ongoing | June Dunnick |
| Aloin | 1415-73-2 | Rats | 13 weeks | Dosed-Water | Ongoing | Mary Boudreau |
| alpha/beta Thujone mixture | 76231-76-0 | Rats | 5 days | Gavage | Initiated | William Gwinn |
| alpha-Pinene | 80-56-8 | Mice, Rats | 2 years | Inhalation | Ongoing | Cynthia Rider |
| Antimony Trioxide | 1309-64-4 | Mice, Rats | 2 weeks | Inhalation | Ongoing | Matt Stout |
| Antimony Trioxide | 1309-64-4 | Mice, Rats | 2 years | Inhalation | Ongoing | Matt Stout |
| AZT/Drug Combinations Transplacental/Neonatal Study | N/A | Mice | 2 years | Gavage | Ongoing | Frederick Beland |
| Bis(2-chloroethoxy)methane | 111-91-1 | Mice | 10 days, 3 days | Gavage | Completed | June Dunnick |
| Bis(2-ethylhexyl) tetrabromophthalate | 26040-51-7 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| Bisphenol AF | 1478-61-1 | Rats | 5 days | Gavage | Initiated | Vicki Sutherland |

| Test Article | CASRN* | Species | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|
| Bisphenol S | 80-09-1 | Mice | 14 days | Dosed-Feed | Initiated | Vicki Sutherland |
| Black Cohosh | 84776-26-1 | Mice | 90 days | Gavage | Ongoing | Michelle Cora |
| Black Cohosh | 84776-26-1 | Mice, Rats | 2 years | Gavage | Ongoing | Chad Blystone |
| Brominated Vegetable Oil | 8016-94-2 | Rats | 90 days | -- | Initiated | Gamboa da Costa |
| Cell Phone Radiation: CDMA | N/A | Mice, Rats | 2 years | Whole Body Exposure | Ongoing | Michael Wyde |
| Cell Phone Radiation: GSM | N/A | Mice, Rats | 2 years | Whole Body Exposure | Ongoing | Michael Wyde |
| Coumarin | 91-64-5 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| Crumbrubber various | N/A | Mice | 14 days | N/A | Initiated | Georgia Roberts |
| Cumene | 98-82-8 | Mice, Rats | 14 days | Inhalation | Ongoing | Georgia Roberts |
| Decabromodiphenyl Ether | 1163-19-5 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| Di(2-ethylhexyl) Phthalate | 117-81-7 | Rats | 2 years | Dosed-Feed | Ongoing | Troy Hubbard |
| Di(2-ethylhexyl) Phthalate | 117-81-7 | Rats | 5 days | Gavage | Initiated | Troy Hubbard |
| Di(2-ethylhexyl) Phthalate | 117-81-7 | Rats | Perinatal + 2 years | Dosed-Feed | Ongoing | Troy Hubbard |
| Dibutyl Phthalate | 84-74-2 | Mice, Rats | 2 years | Dosed-Feed | Ongoing | Chad Blystone |
| Dimethylamine Borane | 74-94-2 | Mice, Rats | 2 weeks | Dermal | Ongoing | Dori Germolec |
| Ephedrine + caffeine combination | N/A | Mice | 10 days, 3 days | Gavage | Completed | June Dunnick |
| Ethinyl estradiol | 57-63-6 | Rats | 2 weeks | Subcutaneous Injection | Ongoing | Todd Auman |
| Ethinyl estradiol | 57-63-6 | Rats | 5 days | Gavage | Initiated | Todd Auman |
| Fenofibrate | 49562-28-9 | Rats | 5 days | Gavage | Initiated | Barry McIntyre |
| Formaldehyde | 50-00-0 | Mice | 2 weeks | Inhalation | Ongoing | Dan Morgan |

| Test Article | CASRN* | Species | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|
| Formaldehyde | 50-00-0 | Mice | 8 weeks | Inhalation | Ongoing | Dan Morgan |
| Furan | 110-00-9 | Rats | 5 days | Gavage | Initiated | Frederick Beland |
| Ginkgo biloba extract | 90045-36-6 | Rats | 5 days | Gavage | Ongoing | Cynthia Rider |
| Goldenseal extract | 84603-60-1 | Rats | 5 days | Gavage | Ongoing | Cynthia Rider |
| Green Tea Extract | N/A | Rats | 5 days | Gavage | Ongoing | Cynthia Rider |
| Hexachlorobenzene | 118-74-1 | Rats | 5 days | Gavage | Initiated | Michael DeVito |
| Hexachlorocyclopentadienyl-dibromocyclooctane | 51936-55-1 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| Indole-3-carbinol | 700-06-1 | Mice, Rats | 2 years | Gavage | Completed | Michael Wyde |
| Insertional Mutagenesis - Definitive Vector Study | N/A | Mice | 14 months | Intravenous | Ongoing | Dori Germolec |
| Ionic Liquid: 1-Butyl-1-methylpyrrolidinium Chloride | 479500-35-1 | Mice, Rats | 90 days | Dosed-Water | Ongoing | Kristen Ryan |
| Ionic Liquid: 1-Butyl-3-methylimidazolium Chloride | 79917-90-1 | Mice, Rats | 90 days | Dosed-Water | Completed | Kristen Ryan |
| Ionic Liquid: 1-Ethyl-3-methylimidazolium Chloride | 65039-09-0 | Mice, Rats | 90 days | Dosed-Water | Ongoing | Kristen Ryan |
| Ionic Liquid: N-Butylpyridinium Chloride | 1124-64-7 | Mice, Rats | 90 days | Dosed-Water | Ongoing | Kristen Ryan |
| Isodecyl Diphenyl Phosphate | 29761-21-5 | Rats | 5 days | Gavage | Ongoing | Scott Auerbach |
| Isopropylated Phenol Phosphate | 68937-41-7 | Mice | 2 weeks | Dosed-Feed | Ongoing | Mamta Behl |
| Isopropylated Phenol Phosphate | 68937-41-7 | Rats | 5 days | Gavage | Ongoing | Scott Auerbach |
| Melamine + Cyanuric Acid combination | N/A | Rats | 90 days | Gavage | Ongoing | Gamboa da Costa |
| Melamine + Cyanuric Acid combination | N/A | Rats | 90 days + recovery | Gavage | Ongoing | Gamboa da Costa |
| Metal Working Fluids: TRIM® VX | N/A | Mice, Rats | 13 weeks | Inhalation | Completed | Kristen Ryan |
| Metal Working Fluids: TRIM® VX | N/A | Mice, Rats | 2 years | Inhalation | Completed | Kristen Ryan |

| Test Article | CASRN* | Species | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|
| Methyleugenol | 93-15-2 | Rats | 5 days | Gavage | Initiated | Michael DeVito |
| Microbiome | N/A | -- | -- | N/A | Ongoing | Carl Cerniglia |
| Milk thistle extract | 84604-20-6 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| Nanoscale Silver | 7440-22-4 | Rats | 13 weeks | Gavage | Completed | Mary Boudreau |
| N-Butylbenzenesulfonamide | 3622-84-2 | Mice | 14 days | Dosed-Feed | Ongoing | Cynthia Rider |
| ortho-Phthalaldehyde | 643-79-8 | Mice, Rats | 90 days | Inhalation | Ongoing | Michael Wyde |
| Pentabromodiphenyl Ether Mixture [DE-71 (Technical Grade)] | 32534-81-9 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| Perfluorohexane sulfonate potassium salt (PFHSKslt) | 3871-99-6 | Rats | 28 days | Gavage | Completed | Chad Blystone |
| Perfluorohexanoic acid (PFHXA) | 307-24-4 | Rats | 28 days | Gavage | Completed | Chad Blystone |
| Perfluorooctanoic Acid | 335-67-1 | Rats | 2 years | Dosed-Feed | Ongoing | Chad Blystone |
| Perfluorooctanoic Acid | 335-67-1 | Rats | 28 days | Gavage | Completed | Chad Blystone |
| Perfluorooctanoic Acid | 335-67-1 | Rats | 5 days | Gavage | Initiated | Chad Blystone |
| Phenolic Benzotriazoles (2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol) | 70321-86-7 | Rats | 14 days | Gavage | Ongoing | Chad Blystone |
| Phenolic Benzotriazoles (2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol) | 25973-55-1 | Rats | 14 days | Gavage | Ongoing | Chad Blystone |
| Phenolic Benzotriazoles (2-(2H-Benzotriazol-2-yl)-4-tert-butylphenol) | 3147-76-0 | Rats | 14 days | Gavage | Ongoing | Chad Blystone |
| Phenolic Benzotriazoles (2-(2H-Benzotriazol-2-yl)phenol) | 10096-91-0 | Rats | 14 days | Gavage | Ongoing | Chad Blystone |
| Phenolic Benzotriazoles (2-(5-Chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)phenol) | 3864-99-1 | Rats | 14 days | Gavage | Ongoing | Chad Blystone |

| Test Article | CASRN* | Species | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|
| Phenolic Benzotriazoles (3-(2H-Benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester) | 84268-23-5 | Rats | 14 days | Gavage | Ongoing | Chad Blystone |
| Phenolic Benzotriazoles (Bumetrizole) | 3896-11-5 | Rats | 14 days | Gavage | Ongoing | Chad Blystone |
| Phenolic Benzotriazoles (Drometrizole) | 2440-22-4 | Rats | 14 days | Gavage | Ongoing | Chad Blystone |
| Phenolic Benzotriazoles (Octrizole) | 3147-75-9 | Rats | 14 days | Gavage | Ongoing | Chad Blystone |
| p-Toluidine | 106-49-0 | Rats | 5 days | Gavage | Ongoing | June Dunnick |
| Pulegone | 89-82-7 | Rats | 5 days | Gavage | Initiated | Scott Auerbach |
| Resveratrol | 501-36-0 | Mice, Rats | 13 weeks | Gavage | Ongoing | Anika Dzierlenga |
| Resveratrol | 501-36-0 | Mice, Rats | 2 weeks | Gavage | Ongoing | Anika Dzierlenga |
| Resveratrol | 501-36-0 | Mice, Rats | 2 years | Gavage | Ongoing | Anika Dzierlenga |
| Sodium Tungstate Dihydrate | 10213-10-2 | Mice, Rats | 2 years | Dosed-Water | Ongoing | Mamta Behl |
| Sulfolane | 126-33-0 | Mice, Rats | 2 years | Dosed-Water | Ongoing | Chad Blystone |
| tert-Butylphenyl Diphenyl Phosphate | 56803-37-3 | Rats | 5 days | Gavage | Ongoing | Scott Auerbach |
| Tetrabromobisphenol A | 79-94-7 | Rats | 13 weeks | Gavage | Ongoing | June Dunnick |
| Tetrabromobisphenol A | 79-94-7 | Rats | 5 days | Gavage | Initiated | June Dunnick |
| Triclosan | 3380-34-5 | Mice | 2 years | Dermal | Ongoing | Jia-Long Fang |
| Triclosan | 3380-34-5 | Rats | 5 days | Gavage | Initiated | Vicki Sutherland |
| Tricresyl Phosphate | 1330-78-5 | Rats | 5 days | Gavage | Ongoing | Scott Auerbach |
| Trimethylsilyldiazomethane (TMSD) | 18107-18-1 | Mice, Rats | 10 days | Inhalation | Ongoing | William Gwinn |
| Triphenyl Phosphate | 115-86-6 | Mice | 2 weeks | Dosed-Feed | Ongoing | Mamta Behl |

| Test Article | CASRN* | Species | Length | Route | Status | Study Scientist |
|---|---|---|---|---|---|---|
| Triphenyl Phosphate | 115-86-6 | Rats | 5 days | Gavage | Ongoing | Scott Auerbach |
| Tris(Chloropropyl)phosphate | 13674-84-5 | Mice, Rats | 2 years | Dosed-Feed | Ongoing | Kristen Ryan |
| Tris(Chloropropyl)phosphate | 13674-84-5 | Mice, Rats | 90 days | Dosed-Feed | Ongoing | Kristen Ryan |
| Tris(Chloropropyl)phosphate | 13674-84-5 | Rats | 5 days | Gavage | Initiated | Kristen Ryan |
| Usnea Lichen | N/A | Mice, Rats | 2 weeks | Dosed-Feed | Ongoing | Julian Leakey |
| Valerian (Valeriana officinalis L.) root extract | 8057-49-6 | Mice | 90 days | Gavage | Ongoing | Troy Hubbard |
| Water disinfection byproducts (Bromodichloroacetic Acid) | 71133-14-7 | Rats | 5 days | Gavage | Initiated | Michael DeVito |

**Related Links:**

Disposition, Metabolism, and Toxicokinetic Studies

Genetic Toxicity Studies

Organ System Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicogenomic Studies

Project Review Committee Approved

## Toxicogenomic Studies

NTP is incorporating the latest toxicogenomic technologies into its testing program to gain further insights into the toxicity of environmental substances. Toxicogenomics examines how the entire genetic structure, or genome, influences an organism's response to environmental toxicants. Microarray, proteomic, metabolomics analyses, and next-generation (NextGen) sequencing are among the advanced technologies that NTP is using to study how chemical exposures change the expression of genes, proteins, and metabolites in targeted cells and tissues.

Measuring genome-wide changes in affected tissues could be useful for identifying disease biomarkers, detecting exposure to toxic substances, and understanding individual genetic susceptibilities. Once validated, biomarkers can be repeatedly sampled during long-term NTP studies to determine if chemical exposures can be detected or if developing diseases (e.g., cancer) provide a genetic signature.

NTP is investigating whether pattern analysis of gene expression can provide toxicity indicators at (1) earlier time points and (2) lower doses than are possible using traditional toxicological parameters. Evaluating patterns of gene expression is expected to provide insight into the pathogenesis of disease and how different rodent models respond to toxicants. In addition, metabolomics provide an opportunity to elucidate how chemicals affect metabolism within cells relative to changes in gene expression.

Several FY 2017 toxicogenomic studies used NextGen sequencing technologies, which improves gene expression analysis, including base pair-level resolution of accuracy and increased sensitivity compared to microarray platforms. Although microarray analysis is a stable and well-understood technology for assaying gene expression, NextGen sequencing methods like RNA-Seq likely will become more common as sequencing costs decline and bioinformatic analyses become standardized and integrated with genomic sequencing.

One promising research area is the application of exome sequencing (Exome-Seq) to either frozen or formalin-fixed, paraffin-embedded tissues. DNA can be extracted from either frozen or archival tissues. Coding portions of DNA, or exons, are captured by libraries of hybridization-based probes targeting over 200,000 exons and transcriptionally active regions. Exon-enriched DNA can be sequenced by DNA-Seq and then genomically aligned to find mutation insertions or deletions and other genetic abnormalities associated with disease.

Several NTP studies are using Exome-Seq for profiling mutations on a genome-wide scale to understand differences between spontaneous and chemically induced tumors. Another promising NextGen sequencing-related area in toxicogenomics is the S1500+ platform. This platform provides a way to use high-throughput transcriptomic (HTT) screening for thousands of genes per sample and can be applied to both in vitro chemical toxicity screening and in vivo screening of RNA extracted from animal tissues.

NTP is evaluating study conditions that could contribute to differential gene expression, such as animal and tissue variability, methods for tissue sampling, and standards for conducting toxicogenomic studies under laboratory conditions. Efforts are underway to optimize methods for DNA and RNA extraction from archival tissues for molecular analysis. Planned or ongoing NTP toxicogenomic studies from FY 2017 are listed below.

## Toxicogenomic Studies Planned or Ongoing in FY 2017

| Chemical (CASRN*) | Species/ Cell Line | Route | Duration | Test Type (Platform) | Study Scientist |
|---|---|---|---|---|---|
| Anthraquinone (84-65-1)<br>Oxazepam (604-75-1)<br>DE-71 (32534-81-9)<br>Dibutyl phthalate (84-74-2)<br>PCTFT (98-56-6)<br>TCPP (115-96-8)<br>Bromodichloroacetic acid (5589-96-8)<br>Ginkgo biloba extract (90045-36-6)<br>Primaclone (125-33-7)<br>Bromochloroacetic acid (5589-96-8) | Mouse | Gavage | 2 years | Infinium DNA methylation bead array | Arun Pandiri |
| Arsenite (7784-46-5) | Human prostate cell line | In vitro | 30 weeks | NextGen sequencing Exome-Seq (Illumina) | Alex Merrick |
| 2,3-Butanedione (diacetyl) (431-03-8)<br>2,3-Hexanedione (3848-24-6) | Human airway epithelium cell line | In vitro | 4 days | High-throughput transcriptomic screening | William Gwinn |
| Bisphenol A and analogs (80-05-7) | Human hepatocyte cell line | In vitro | 2 days | High-throughput transcriptomic screening | Mike DeVito |
| BPAF (1478-61-1)<br>TBBPA (79-94-7) | Rat | Gavage | 5 days | S1500+ NextGen sequencing | Sue Fenton |
| Bromodichloroacetic acid (5589-96-8)<br>Methyleugenol (93-15-2)*** | Mouse | Gavage | 2 years | NextGen sequencing Exome-Seq (Illumina) | Arun Pandiri |
| Dieldrin (60-57-1)<br>Ethinyl estradiol (57-63-6)<br>Methyl mercury (115-09-3)<br>Rotenone (83-79-4)<br>Phenol (68937-41-7)<br>Isopropylated phosphate (3:1) (60348-60-9)<br>Pentabromodiphenyl ether (60348-60-9) | Mouse | In vitro | 1 day | S1500+, NextGen sequencing | Alison Harrill |
| DE-71 (32534-81-9)<br>PCB-126 (57465-28-2)<br>Phenobarbital (50-06-6)*** | Rat | Gavage | GD** to PND 22 | Microarray (Affymetrix) | June Dunnick |

| Chemical (CASRN*) | Species/ Cell Line | Route | Duration | Test Type (Platform) | Study Scientist |
|---|---|---|---|---|---|
| Phosphate flame retardants:<br>tert-Butylphenyl diphenyl phosphate (56803-37-3)<br>2-Ethylhexyl diphenyl phosphate (1241-94-7)<br>Isodecyl diphenyl phosphate (29761-21-5)<br>Isopropylated phenol phosphate (68937-41-7) | Rat | Gavage | 5 days | Microarray (Affymetrix)<br>Metabolomics | Scott Auerbach |
| Ginkgo biloba extract (90045-36-6) | Rat | Gavage | 5 days | Microarray (Affymetrix) | Cynthia Rider, Scott Auerbach |
| Induced Pluripotent Stem Cells<br>Embryoid bodies<br>Embryonic stem cells | Human stem cell | N/A | N/A | High-throughput transcriptomic screening | Erik Tokar, Mike DeVito |
| N/A | Rat | N/A | 2 years | Targeted resequencing | Arun Pandiri, Ramesh Kovi |
| 2-Hydroxy-4- methoxybenzophenone (131-57-7) | Rat | Oral (food) | 90 days | Microarray (Affymetrix) | Scott Auerbach |
| Methyleugenol extract (93-15-2)<br>Ginkgo biloba extract (90045-36-6)*** | Mouse | Gavage | 2 years | NextGen sequencing Exome-Seq RNA-Seq (Illumina) | Arun Pandiri, Scott Auerbach, Alex Merrick |
| PCB-11 (2050-67-1) | Rat<br>Human hepatocyte cell line | In vitro | 1 day | S1500+ NextGen sequencing | Mike DeVito |
| 2,3-Pentanedione (600-14-6) | Rat | Inhalation | 14 and 28 days | microRNA Microarray (Affymetrix) | Dan Morgan |
| PBDE-47 (32534-81-9) | Rat | Gavage | 21 days | Microarray | June Dunnick |
| Polycyclic aromatic compounds:<br>Acenaphthenequinone (82-86-0)<br>Benzo[b]fluoranthene (205-99-2)<br>Benzo(a)pyrene (50-32-8)<br>Dibenz[a,h]anthracene (53-70-3)<br>9-Methylanthracene (779-02-2)<br>1-Methylfluorene (1730-37-6)<br>Perinaphthenone (548-39-0)<br>Phenanthrene (85-01-8)<br>Pyrene (129-00-0) | Human hepatocyte cell line | In vitro | 2 days | Cytotoxicity<br>Gene expression by quantitative polymerase chain reaction | Cynthia Rider, Erik Tokar |

| Chemical (CASRN*) | Species/ Cell Line | Route | Duration | Test Type (Platform) | Study Scientist |
|---|---|---|---|---|---|
| 2,2',4,4',5-Pentabromodiphenyl ethers (5436-43-1)<br>Pentabromodiphenyl oxide (technical) (DE-71) (32534-81-9)<br>3,3,4,4,5- Pentachlorobiphenyl (57465-28-8)<br>2,2'4,4'- Tetrabromodiphenyl ether (DE-47) (5436-43-1) | Rat<br>Mouse | Gavage | GD** 6 through 3 weeks | Microarray (Affymetrix) | June Dunnick |
| Tetrabromobisphenol A (79-94-7)<br>BDE-47 (5436-43-1)<br>Pentabromodiphenyl oxide-technical (DE-71) (32534-81-9) | Rat | Gavage | GD** 6 through 3 weeks | Microarray (Affymetrix) | Arun Pandiri, Ramesh Kovi |
| Tetrabromobisphenol A (79-94-7)<br>Pentabromodiphenyl oxide-technical (DE-71) (32534-81-9)<br>Triclosan (3380-34-5)<br>alpha, beta-Thujone (76231-76-0) | Rat | Gavage | 5 days | High-throughput transcriptomic screening | Mike DeVito, William Gwinn |
| 112-chemical compound test set (pharmaceuticals and environmental compounds) | Human hepatocyte cell line-HepaRG | In vitro | 2 days | High-throughput transcriptomic screening | Stephen Ferguson, Sreenivasa Ramaiahgari |
| 20-chemical compound test set (environmental compounds) | Primary rat hepatocytes Human HepaRG cells | In vitro | 3 days | S1500+ NextGen sequencing | William Gwinn, Mike DeVito |
| Time-restricted feeding<br>Shift work-surrogate study | Rat | In vivo | 4 months | Microarray | Gopi Gadupudi, Arun Pandiri |

*Chemical Abstracts Service Registry Number
**GD: gestational day
***This study will compare toxicogenomic effects among the chemicals listed together.

**Related Links:**

Disposition, Metabolism, and Toxicokinetic Studies
Genetic Toxicity Studies
Organ System Toxicity Studies
Modified One-Generation Reproduction Studies
Toxicology and Carcinogenicity Studies
Project Review Committee Approved

## Project Review Committee Approved

The table below lists studies that were approved by either the internal NIEHS/NTP protocol approval committee or the internal NIEHS/NTP project review committee, but were not started during FY 2017.

| Protocol Title | Study Scientists |
|---|---|
| Prenatal Toxicity Study of 2-{[1-(4-Phenoxyphenoxy)propan-2-yl]oxy}pyridine in New Zealand White Rabbits Exposed Via Gavage | Vicki Sutherland/ Barry McIntyre |
| Toxicokinetic Studies (K03014) of α-Pinene (CAS 80-56-8, Test Article M030014) in Hsd:Sprague Dawley SD Rats and B6C3F1/N Mice Exposed Via Whole Body Inhalation | Cynthia Rider |
| Investigative Mammary and Reproductive Endpoint Studies of α-Pinene in Hsd:Sprague Dawley SD Rats Exposed Via Whole Body Inhalation | Cynthia Rider |
| Modified One-Generation (MOG) Dose Range-Finding Study (MOG00056) of Microcystin LR (CAS# 101043-37-2, M000056) in CD1 Mice Exposed Via Oral Gavage | Vicki Sutherland/ Barry McIntyre |
| Developmental Immunotoxicity Evaluation (# I10482B) of N-Butylbenzenesulfonamide (NBBS, CAS #3622-84-2, Test Article #10057) in Sprague Dawley (HSD: Harlan Sprague Dawley SD) Rats Exposed Via Dosed Feed | Kelly Shipkowski/ Cynthia Rider |
| Modified One-generationStudy (MOG 16001B) of Echinacea Purpurea Root Extract (CAS #90028-20-9,Test Article #16001) in Sprague Dawley (Hsd:Harlan Sprague Dawley SD) Rats Exposed via Gavage | Kristen Ryan |

**Related Links:**

Disposition, Metabolism, and Toxicokinetic Studies

Genetic Toxicity Studies

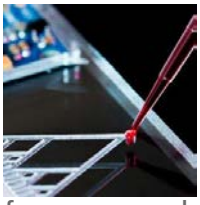
Organ System Toxicity Studies

Modified One-Generation Reproduction Studies

Toxicology and Carcinogenicity Studies

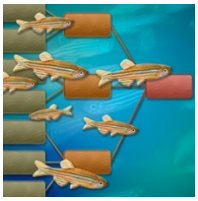
Toxicogenomic Studies

# NICEATM



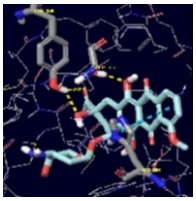
## About NICEATM

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) supports the development and evaluation of new, revised, and alternative methods to identify potential hazards to human health and the environment, with a focus on replacing, reducing, or refining animal use.



## NICEATM Webinars and Workshops

A summary of webinars and workshops held or supported by NICEATM in FY 2017.



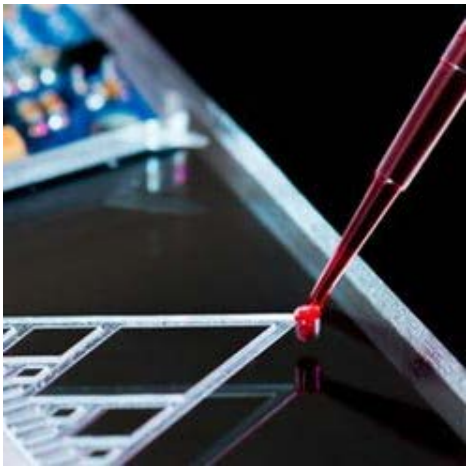
## NICEATM Support of Tox21

A description of Tox21 projects NICEATM supported in FY 2017.

## Additional NICEATM Activities

A summary of other activities NICEATM has conducted and participated in during FY 2017.

# About NICEATM



The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) supports the development and evaluation of methods for identifying potential hazards to human health and the environment that could replace, reduce, or refine animal use.

NICEATM activities include:

- Conducting and publishing analyses and evaluations of data from new, revised, and alternative testing approaches.
- Providing information to test method developers, regulators, and regulated industry through its website and other communications and by organizing workshops and symposia.
- Coordinating and providing logistical support for the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) meetings, webinars, teleconferences, working groups, and public forums.
- Providing bioinformatics and computational toxicology support to NIEHS/NTP projects, especially those related to Tox21.

Warren Casey, Ph.D., is director of NICEATM. NICEATM receives contract support from Integrated Laboratory Systems, Inc.

**Related Annual Report Pages:**

FY 2017 NICEATM Webinars and Workshops

NICEATM Support of Tox21

Additional NICEATM Activities

## Related Links

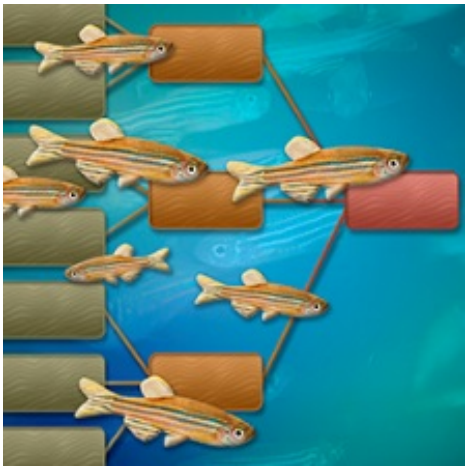
Activities and Resources

Publications

Reports

# NICEATM Webinars and Workshops

## Webinar Series: Using Informatics to Improve Data Analysis of Chemical Screening Assays Conducted in Zebrafish



NICEATM presented a webinar series in February and March 2017 as part of the NTP Systematic Evaluation of the Application of Zebrafish in Toxicology initiative. Zebrafish is a useful vertebrate model for toxicological screening studies because of its small size and rapid development, but a lack of harmonization in several key protocol components hinders the model's broader adoption. This webinar series examined how variability in protocols for toxicological screening studies using zebrafish might be addressed by implementing standardized nomenclature systems or ontologies.

The webinar series was open to the public and viewed by over 100 participants. The webinars also provided information on an April 2017 meeting at NIEHS where expert investigators and data scientists discussed how to improve zebrafish screening data analysis by implementing ontologies. A report from the meeting describing recommendations on best practices and identifying technology development and other needs is planned for publication in FY 2018.

Presentations from the webinar series are available on the NTP website.

## BioMed 21 Workshop

NICEATM and the Human Toxicology Project Consortium organized a June 2017 workshop, BioMed21 – A Human Pathway-based Approach to Disease and Medicine.

Recognition is growing for the need for greater focus on human-relevant data to increase the success rate of drug development. Such data will support implementation of methods to assess chemical toxicity that are based on human biological pathways. Several international projects are underway to mine literature, collect data, and organize data into adverse outcome pathways. This workshop assembled representatives from several of these projects to identify barriers and opportunities for improvement and to recommend support for implementation of a human systems biology platform to understand disease and improve interventions.

More information about the workshop is available on the NTP website.

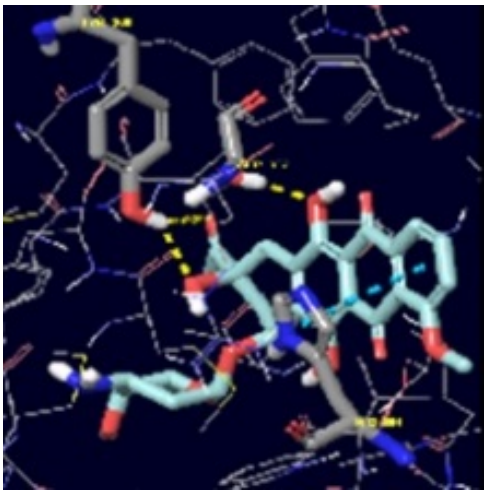
**Related Annual Report Pages:**

About NICEATM

NICEATM Support of Tox21

Additional NICEATM Activities

# NICEATM Support of Tox21



The Tox21 research initiative aims to improve regulatory hazard assessment of substances potentially harmful to humans and the environment. Tox21 uses in vitro high-throughput screening assays to evaluate the biological activity of compounds in a 10,000 compound library and to map the observed activities to toxicity pathways.

One goal of Tox21 is to incorporate in vitro assay data into models that can be used to predict toxic (or adverse) effects in humans resulting from chemical exposures. NICEATM provides support to the Tox21 effort primarily through its computational toxicology group. Specific NICEATM projects in support of Tox21 are included in the Tox21 Projects section.

**Related Annual Report Pages:**

About NICEATM

FY 2017 NICEATM Webinars and Workshops

Additional NICEATM Activities

# Additional NICEATM Activities

## Acute Systemic Toxicity

Alternative models developed for estimating acute systemic toxicity generally are evaluated using in vivo LD50 values, but variability in the values makes such assessments challenging. To characterize this variability more fully, NICEATM and collaborators at the Environmental Protection Agency (EPA) National Center for Computational Toxicology compiled a large data set of acute oral LD50 values from several curated databases.

Some chemicals having multiple LD50 values exhibited high variability, with some values ranging across multiple orders of magnitude. Such variability, which confounds hazard categorization, underscores the importance of considering an appropriate margin of uncertainty when using in vivo oral acute toxicity data to assess the performance of alternative methods. The analysis of the full data set will be presented at the 2018 Society of Toxicology meeting, and a manuscript describing the analysis is in preparation for publication in 2018.

## Developmental Toxicity

NICEATM is working with other National Toxicology Program (NTP) scientists at NIEHS to compile a list of developmental toxicants that cover developmental outcomes ranging from subtle effects such as fetal weight changes through post-implantation loss. Toxicants are selected based on the availability of “high-quality” studies, those appropriately designed and powered with relevant endpoints that cover likely different modes of action.

After further evaluation and assessment, the studies are used to identify and extract data. Identified toxicants are candidates for testing with in vitro assays using primary cells, stem cells, or cell lines and for conducting in vivo assays using lower-order organisms such as zebrafish or roundworm (*Caenorhabditis elegans*). Test results will be compared to available in vivo mammalian data from rodents, rabbits, and humans. The toxicant list is being constructed with input from experts in industry, academia, and government and is expected to include agrochemicals, pharmaceuticals, and other chemicals.

## Endocrine Disruptors

NICEATM is collaborating with test method developer CertiChem, Inc., to validate an in vitro test method that uses MDA-Kb2 human breast cancer cells to measure androgen receptor agonist and antagonist activity. Testing of 67 coded reference chemicals in agonist and antagonist modes to characterize method reliability and relevance is anticipated to be completed in early FY 2018. Then, 30 additional consumer products will be tested to evaluate the method’s applicability for more than single chemicals.

## Skin Sensitization

NICEATM and ICCVAM scientists developed integrated testing strategies that use non-animal data to predict skin sensitization hazard. Three manuscripts published in FY 2016 and FY 2017 describe strategies for using non-animal data to predict outcomes of animal skin sensitization tests, human skin sensitization tests, and human or animal tests for skin sensitization potency classification.

The NTP Toxicology Branch is testing over 200 chemicals nominated by ICCVAM agencies using three in vitro test methods to expand the applicability of a defined approach for identifying skin sensitizers. Mouse local lymph node assay data are available for the nominated chemicals, which include pesticides, formulations, industrial chemicals, and other chemicals of interest to ICCVAM agencies. The three in vitro test methods are the LuSens method, the direct peptide reactivity assay, and the human cell line activation test. NICEATM is coordinating the testing, which began in 2016 and is scheduled for completion in early 2019. The study data will enable NICEATM and ICCVAM to

evaluate the appropriateness of a defined approach using these three in vitro methods for various regulatory applications.

NICEATM collaborated with the Cosmetics Europe Skin Tolerance Task Force to evaluate integrated testing and assessment approaches for skin sensitization submitted to the Organisation for Economic Co-operation and Development. NICEATM evaluated six defined approaches with a set of previously untested chemicals having in vitro and in silico data provided by Cosmetics Europe. Manuscripts describing the data sets and the outcome of the analyses have been submitted for publication.

## Ocular Irritation

NICEATM and the PETA International Science Consortium are proposing a joint study to evaluate the utility and limitations of a group of in vitro test methods to identify the ocular irritation and corrosion potential of agrochemicals. Coded pesticide formulations donated by agrochemical companies will be tested to describe each method's performance characteristics and determine which methods could be combined with in vitro defined approaches to assign hazard classification and labeling for eye irritation potential. Although the focus of this study will be on EPA hazard classification, study results also will be evaluated for classification and labeling under the United Nations Globally Harmonized System of Classification and Labelling of Chemicals. Testing will begin in 2018.

## Integrated Chemical Environment

Successful computational toxicology projects depend on freely available, high-quality data that are formatted for use in computational workflows. The NICEATM Integrated Chemical Environment (ICE) resource, launched in March 2017, provides high-quality, curated data from NICEATM, its partners, and other resources and tools to facilitate chemical safety assessment.

At the end of FY 2017, ICE included data from animal and non-animal tests that assessed regulatory endpoints such as acute oral toxicity, skin and eye irritation, skin sensitization, and endocrine activity. It also included curated high-throughput screening data from Tox21 and physicochemical property data on chemicals such as solubility, melting point, and molecular weight. The site offers downloadable workflows for predicting physicochemical properties, skin sensitization potency, and adverse outcome pathway mapping. ICE is open to all users, with no registration needed.

Updates to ICE in FY 2018 will add formulation data and allow users to compare labeling categories from EPA "six-pack" studies with the performance of the formulation's active ingredients in non-animal methods. Additional updates will expand the offered in silico prediction models and computational workflows to include in vitro-to-in vivo extrapolation and characterization of chemicals from the ICE website and through downloadable workflows.

**Related Annual Report Pages:**

About NICEATM

FY 2017 NICEATM Webinars and Workshops

NICEATM Support of Tox21

# ICCVAM


## About ICCVAM

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is a permanent interagency committee of NIEHS.


## A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States

ICCVAM is coordinating the development of a strategic roadmap to adopt new approaches to safety and risk assessment of chemicals and medical products that improve human relevance and replace or reduce the use of animals.

## ICCVAM Meetings

A description of meetings held by ICCVAM in FY 2017.

## ICCVAM Test Method Evaluation Activities

A list of NICEATM and ICCVAM test method evaluation activities in FY 2017.

## ICCVAM International Validation Activities

A description and list of NICEATM and ICCVAM international validation activities in FY 2017.

# About ICCVAM

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is a permanent interagency committee of NIEHS under NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). Established by the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3), its purpose is "to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness."

ICCVAM is composed of representatives from 16 U.S. federal regulatory and research agencies that generate or use toxicological and safety testing information. Warren Casey, Ph.D., serves as administrative director of ICCVAM.

**Related Annual Report Pages:**

Strategic Roadmap for New Approaches to Evaluate the Safety of Chemicals and Medical Products

ICCVAM Meetings

ICCVAM Test Method Evaluation Activities

ICCVAM International Validation Activities

## ICCVAM Member Agencies

**ATSDR** (HHS/CDC)
Agency for Toxic Substances and Disease Registry

**CPSC**
Consumer Product Safety Commission

**DOD**
U.S. Department of Defense

**DOE**
U.S. Department of Energy

**DOI**
U.S. Department of the Interior

**DOT**
U.S. Department of Transportation

**EPA**
U.S. Environmental Protection Agency

**FDA** (HHS)
U.S. Food and Drug Administration

**NCI** (HHS/NIH)
National Cancer Institute

**NIEHS** (HHS/NIH)
National Institute of Environmental Health Sciences

**NIH (HHS)**
National Institutes of Health

**NIOSH (HHS/CDC)**
National Institute for Occupational Safety and Health

**NIST** (DOC)
National Institute of Standards and Technology

**NLM** (HHS/NIH)
National Library of Medicine

**OSHA** (DOL)
Occupational Safety and Health Administration

**USDA**
United States Department of Agriculture

## Related Links

Information on ICCVAM Activities

Complete list of articles on ICCVAM activities published in scientific journals

# A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States

During FY 2017, ICCVAM coordinated the development of a strategic roadmap for incorporating new approaches into safety testing of chemicals and medical products in the United States. Sixteen federal agencies and multiple interagency workgroups, with input from a broad range of stakeholder groups, developed the roadmap.


The roadmap creates a framework that guides the development of enabling technologies and promotes strategies to establish confidence in and ensure utilization of new approaches to toxicity testing that improve human health relevance and reduce or eliminate the need for testing in animals. The successful development and implementation of these new approaches will require coordinated efforts that address three strategic goals:

1. Connect users with developers of new approach methodologies.
2. Foster the use of efficient, flexible, and robust practices to establish confidence in new methods.
3. Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries.

The roadmap was first proposed to the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) in 2015. SACATM expressed support for the development of the roadmap as an ICCVAM activity at its September 2016 meeting. A meeting of ICCVAM members and other federal employees in February 2017 established an outline for the roadmap. Opportunities for public comment during development of the roadmap occurred during the annual meeting of the Society of Toxicology in March, ICCVAM Public Forum in May, NTP Board of Scientific Counselors meeting in June, and SACATM meeting in September.

The final roadmap document was published in January 2018 and is available on the NTP website.

Activities are underway to address the roadmap goals. Presentations at the September 2017 SACATM meeting described implementation of the roadmap for skin sensitization and acute systemic toxicity testing. Reviews of U.S. agency information requirements for these areas are being prepared and are planned for publication in FY 2018.

## Related Links

Information on ICCVAM Activities

Complete list of articles on ICCVAM activities published in scientific journals

**Related Annual Report Pages:**

About ICCVAM

ICCVAM Meetings

ICCVAM Test Method Evaluation Activities

ICCVAM International Validation Activities

# ICCVAM Meetings

NICEATM supported six teleconferences and three in-person meetings held by ICCVAM in FY 2017. These included one in-person meeting and three teleconferences of ICCVAM representatives developing "A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States."

NICEATM also supported seven ad hoc ICCVAM workgroups focused on acute systemic toxicity, ocular and dermal irritation, developmental and reproductive toxicity, skin sensitization, use of read-across in toxicity testing applications, in vitro-to-in vivo extrapolation, and identification and characterization of reference chemicals for validation of in vitro endocrine disruptor assays.

The third ICCVAM Communities of Practice webinar was held on January 24, 2017. The webinar emphasized the importance of understanding the structural and functional diversity of chemical sets used in developing and validating alternative approaches to traditional in vivo toxicology test methods. Denis Fourches, Ph.D., of North Carolina State University described chemoinformatics methods for predicting toxicity. Kamel Mansouri, Ph.D., of the Environmental Protection Agency (EPA) presented case studies on how such methods have been successfully applied. Slide presentations from the webinar are available on the NTP website.

ICCVAM, with NICEATM support, held its fourth public forum on May 23, 2017, at the National Institutes of Health (NIH) in Bethesda, Maryland. Representatives from 10 ICCVAM member agencies were joined by attendees representing stakeholder groups and over 100 webcast viewers. ICCVAM members provided information about their agency activities on the development and validation of test methods and approaches that could replace, reduce, or refine animal use. Stakeholder groups suggested areas to be addressed and encouraged development of the strategic roadmap. The agenda and presentations are available on the NTP website.

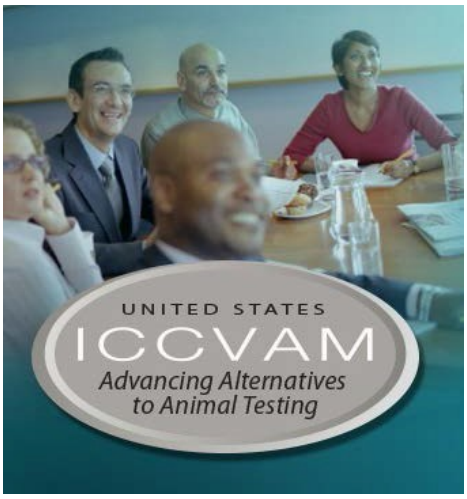
**Related Annual Report Pages:**

About ICCVAM

Strategic Roadmap for New Approaches to Evaluate the Safety of Chemicals and Medical Products

ICCVAM Test Method Evaluation Activities

ICCVAM International Validation Activities




## Related Links

Information on ICCVAM Activities

Complete list of articles on ICCVAM activities published in scientific journals

# ICCVAM Test Method Evaluation Activities

ICCVAM received no formal test method nominations or submissions in FY 2017. ICCVAM welcomes submissions of innovative test methods that might be acceptable for specific regulatory use and for which adequate validation studies have been completed. To maximize effective implementation of new test methods or approaches, however, ICCVAM evaluates and recommends only those test methods proposed for regulatory uses that align with ICCVAM member agencies' needs and priorities. More information on ICCVAM test method submissions is available. ICCVAM test method evaluation activities in FY 2017 are summarized below.

## Test Method Evaluation Activities in FY 2017

| Test Method | ICCVAM Recommendations/Agency Status |
|---|---|
| ICCVAM integrated decision strategy for skin sensitization | ICCVAM developed integrated decision strategies using in vitro, in chemico, and in silico information based on an established skin sensitization adverse outcome pathway. Following publication in FY 2016 of two manuscripts describing strategies to predict animal and human skin sensitization of test results, a third manuscript describing a strategy to predict animal and human skin sensitization potency was published in FY 2017. |
| Electrophilic allergen screening assay | This test method, nominated by the National Institue for Occupational Safety and Health (NIOSH), is an in chemico assay intended to identify potential skin sensitizers. A validation study of the method began in FY 2017 with four ICCVAM agencies participating in the study. NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) coordinates the study, and members of the ICCVAM Skin Sensitization Workgroup serve on the study management team. Current efforts focus on testing a small group of blinded chemicals for a preliminary assessment of accuracy and reproducibility. The study is expected to continue through the end of FY 2018. |
| OptiSafe | NICEATM is coordinating a multilaboratory validation study to determine the reliability and relevance of the OptiSafe test method. In this method, a test substance is applied to a semipermeable membrane to assess the substance's potential to cause eye irritation. Three participating laboratories completed testing of 30 chemicals in FY 2017. In FY 2018, the nominating laboratory will complete testing on 60 additional coded chemicals to expand the applicability of the method. |
| EpiAirway | A cooperative agreement under the NIEHS Phase IIb Small Business Innovation Research is providing funding to MatTek Corporation to validate its EpiAirway™ in vitro human bronchial tissue model to predict the toxicity of inhaled chemicals. Several ICCVAM agency representatives are members of the cooperative agreement steering committee. In FY 2017, the steering committee recommended test chemicals to expand the domain of applicability, making EpiAirway™ more relevant to their respective agencies, and test chemicals are being procured. NICEATM provides scientific oversight of this NIEHS small business program supporting validation of alternative test methods. |

The 16 member agencies of ICCVAM are engaged in additional activities that support replacing, reducing, and refining animal use. Summaries of these additional activities can be found on the NTP website.

**Related Annual Report Pages:**

About ICCVAM

Strategic Roadmap for New Approaches to Evaluate the Safety of Chemicals and Medical Products

ICCVAM Meetings

ICCVAM International Validation Activities

# ICCVAM International Validation Activities

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and ICCVAM participate in international test method validation activities through the Organisation for Economic Co-operation and Development (OECD) and collaborate with member countries of the International Cooperation on Alternative Test Methods (ICATM), including the European Union, Japan, Korea, and Canada.

In FY 2017, ICCVAM agencies commented on draft OECD documents through the U.S. National Coordinator for the OECD Test Guidelines Programme, an ex officio ICCVAM member. NICEATM and ICCVAM collaborated with international colleagues on a revision of the acute dermal toxicity test guideline (Test Guideline 402), adopted by OECD in 2017. A NICEATM scientist also served on a peer-review panel updating Test Guideline 442B for non-radiolabeled murine local lymph node assay methods.

Representatives of NICEATM and ICCVAM attended meetings of the OECD expert groups on eye irritation and skin sensitization in FY 2017.

ICATM collaborations address three critical areas of cooperation: test method validation studies, independent peer review of validation studies, and development of formal recommendations on alternative testing methods. Representatives of NICEATM and ICCVAM attended an ICATM coordination meeting and ICATM-sponsored workshop to develop criteria for evaluating non-animal approaches for skin sensitization potential in October 2016.

Representatives of NICEATM and ICCVAM also attended an October 2016 workshop sponsored by ICATM. Products of this workshop include a white paper characterizing international regulatory requirements for skin sensitization testing (to be submitted for publication in FY 2018), a position paper covering workshop outcomes and ICATM recommendations (accepted for publication in FY 2018), and a proposal to develop a performance-based test guideline for defined approaches to testing and assessment of skin sensitization, which was accepted by OECD in April 2017.

Ongoing international validation studies led by ICATM member organizations that include NICEATM or ICCVAM participants are listed below.

## Participation in International Validation Studies

| Test Method | Test Type | Lead Organization* | NICEATM-ICCVAM Involvement |
|---|---|---|---|
| IL-8 in vitro test for assessing skin sensitization potential | Allergic contact dermatitis | JaCVAM | Study is complete; an ICCVAM member served on a peer-review panel. |
| Vitrigel-SST assay for assessing skin sensitization potential | Allergic contact dermatitis | JaCVAM | NICEATM staff are serving on the validation management team; study is currently on hold. |
| Vitrigel-EIT assay for eye irritation testing | Ocular irritation | JaCVAM | Study is complete; an ICCVAM member served on a peer-review panel. |
| Hand1-luc in vitro test for assessing reproductive toxicity potential | Reproductive toxicity | JaCVAM | Study is complete, and ICCVAM members served on a peer-review panel. |
| SIRC-CVS assay for eye irritation testing | Ocular irritation | JaCVAM | Study is complete; an ICCVAM member served on a peer-review panel. |

| Test Method | Test Type | Lead Organization* | NICEATM-ICCVAM Involvement |
|---|---|---|---|
| Amino acid derivation reactivity assay | Allergic contact dermatitis | JaCVAM | NICEATM staff served on the validation management team; a peer review of the study is scheduled for spring 2018. |

*Japanese Center for the Validation of Alternative Methods

**Related Annual Report Pages:**

About ICCVAM

Strategic Roadmap for New Approaches to Evaluate the Safety of Chemicals and Medical Products

ICCVAM Meetings

ICCVAM Test Method Evaluation Activities

# Literature Analysis

## Noncancer Research

NTP conducts evaluations to assess the evidence that substances cause adverse health effects and provides opinions on whether these substances could be of human concern.


## Report on Carcinogens

The Report on Carcinogens is a congressionally mandated listing of substances that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and to which a significant number of persons residing in the United States are exposed.

# Noncancer Research

NTP has made a commitment to studying noncancer health effects. As part of that commitment, NTP assesses the evidence that environmental chemicals, physical substances, or mixtures—collectively referred to as substances—cause adverse health effects. NTP also provides opinions on whether these substances might be of concern, given what is known about current human exposure levels. The Office of Health Assessment and Translation (OHAT) conducts health hazard assessments and scoping reviews or state-of-the-science evaluations, which are published as NTP monographs, NTP research reports, and journal publications. OHAT also hosts workshops to address important issues in environmental health sciences. Andrew Rooney, Ph.D., served as acting director of OHAT in FY 2017.

In FY 2017, NTP published the NTP Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate, the first evaluation reaching hazard conclusions using the OHAT Approach to Systematic Review and Evidence Integration. OHAT began using a new data visualization format—an interactive systematic evidence map—that allows readers to search and explore evidence categorized by health effect, exposure, and type such as the literature collected in the state-of-the-science evaluation of transgenerational inheritance.

As part of efforts to promote harmonization in development of systematic review methods, OHAT hosted the 4th International Symposium on Systematic Review and Meta-Analysis of Laboratory Studies in April 2017. OHAT also published several reports in the new NTP research report series, including a pilot study on tin and organotin levels in Danish women, a systematic review of biological activity of bisphenol A structural analogues, and a systematic review of the effects of fluoride on learning and memory in animal studies.

## Ongoing Noncancer Health Effects Projects

| Project & Study Scientist | Project Summary |
|---|---|
| Evaluation of long-term neurological effects of acute exposure to the organophosphorus nerve agent sarin<br><br>Study Scientist: Andrew Rooney | Sarin is a highly toxic organophosphorus nerve agent developed for chemical warfare during World War II that continues to be used as a weapon today. The immediate, or acute, effects of sarin exposure are serious and well known, including constriction of the pupils, muscle paralysis, seizures, cardiorespiratory depression, and death due to respiratory failure. Although there are reports of potential long-term neurological effects from sarin exposure, the evidence has not been evaluated with the increased objectivity, rigor, and transparent process of a systematic review methodology. In partnership with the NIH Countermeasures Against Chemical Threats (CounterACT) Program, NTP is conducting a systematic review to evaluate the evidence for long-term neurological effects in humans following acute exposure to sarin. The protocol was posted in April 2017, and this evaluation is ongoing. |
| Evaluation of inflammation-based atherosclerosis associated with environmental exposures<br><br>Study Scientists: Andrew Rooney and Brandy Beverly | Evidence is growing that the environment plays a role in a wide range of diseases that involve inflammation. The extent to which environmental exposures ultimately lead to these adverse health effects through an inflammatory pathway remains unclear. This evaluation will examine the evidence that environmental substances contribute to inflammation, which ultimately leads to atherosclerosis, and will identify biomarkers of the inflammation involved. Atherosclerosis was selected for investigation because of the significant public health impact of the disease, and the well-established role for inflammation in the disease process that leads to it. The concept was reviewed at the December 2014 Board of Scientific Counselors meeting, and the evaluation has been initiated. |

| | |
|---|---|
| NIEHS-EPA pilot study of exposure to chemicals in consumer products<br><br>Study Scientist: Kyla Taylor | Concern has been raised about the endocrine-disrupting potential of some chemicals found in personal care and other consumer products. Given the large number of co-occurring chemicals in these products, new strategies and techniques need to be developed. NIEHS is collaborating with EPA to perform a small-scale, longitudinal pilot study to evaluate the performance of existing survey, measurement, and modeling methods for assessing exposures to chemicals in several consumer product categories, including personal and child care, household cleaning, lawn and garden, home improvement, and food packaging products. The pilot study addresses several research needs related to the measurement and modeling of human exposures. The concept was reviewed at the June 2015 Board of Scientific Counselors meeting, and the NIEHS Institutional Review Board (IRB) for the Protection of Human Subjects in Research has approved the project. This study is currently open for enrollment. |
| State of the science for transgenerational inheritance of health effects<br><br>Study Scientist: Vickie Walker | Transgenerational inheritance is the phenomenon in which an individual's exposures have far-reaching consequences, affecting multiple generations removed from the original insult. NTP conducted a state-of-the-science or scoping review to examine the evidence for transgenerational inheritance of health effects associated with exposure to a wide range of stressors (e.g., environmental chemicals, drugs of abuse, nutrition and diet, pharmaceuticals, infectious agents, stress) in humans and animals. The report systematically compiled and categorized the literature to develop an evidence map for transgenerational inheritance by broad health-effect categories, exposures, and types of evidence, and identified areas of consistency, uncertainty, data gaps, and research needs. Evidence mapping illustrated that risk of bias, having generally few studies, and heterogeneity in exposures and endpoints examined present serious limitations to available bodies of evidence for assessing transgenerational effects. This report was accepted for publication in Environment International in December 2017. |
| Evaluation of children's health and traffic-related air pollution<br><br>Study Scientists: Kembra Howdeshell and Brandy Beverly | Research on traffic-related air pollution and children's health has increased in the past decade, reflecting improvement in air monitoring technology and exposure methodology. Traffic-related air pollution has been measured in multiple ways, including direct traffic measures (such as traffic proximity or density) and surrogate measures of traffic-related air pollution (such as particulate matter, oxides of nitrogen, and other products of fossil-fuel combustion generated by motor vehicles including benzene, diesel exhaust, and polycyclic aromatic hydrocarbons). This topic is the subject of a series of evaluations on the evidence for an association between traffic-related air pollution and health outcomes impacting the fetus and children, beginning with hypertensive disorders of pregnancy and neurological development and function in children. The concept was reviewed at the April 2014 Board of Scientific Counselors meeting. The protocol was posted in June 2016, and the evaluation is ongoing. |
| Evaluation of adverse health effects and occupational exposure to cancer chemotherapy agents<br><br>Study Scientist: Kembra Howdeshell | Cancer chemotherapy agents are cytotoxic drugs, many of which are known mutagens and developmental toxicants. Occupational exposure to cancer chemotherapy agents can occur in various professions including medical, veterinary, and manufacturing. Although improved handling procedures and engineering controls have reduced contamination, surface contamination persists in pharmacy and nursing areas of some hospital-based cancer centers. This evaluation examined the evidence that occupational exposure to cancer chemotherapy agents is associated with adverse health effects, including genetic toxicity, cancer, reproductive and developmental effects, and acute effects. The concept was reviewed at the April 2014 Board of Scientific Counselors meeting and the protocol posted in October 2015. The draft NTP monograph has been completed and is undergoing peer review. |

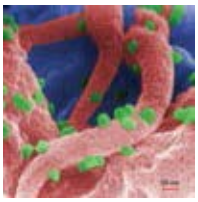
| | |
|---|---|
| Biological activity of bisphenol A (BPA) structural analogues and functional alternatives<br><br>Study Scientist: Katie Pelch | Bisphenol A (BPA) is a high production volume chemical used in the manufacture of polycarbonate plastic, thermal paper, dental resins, and other composite materials used in consumer products. Recent studies report widespread use and exposure to a variety of chemicals with structural or functional similarity to BPA, referred to as BPA analogues. This study reviews human, animal, and in vitro evidence that the biological activity of BPA analogues is an emerging public health concern. The topic will be addressed further through in vitro laboratory experiments and external collaborations to evaluate in vivo activity in two model organisms, zebrafish and *Caenorhabditis elegans*. The concept was reviewed at the June 2015 Board of Scientific Counselors meeting. The protocol was finalized in August 2015, and the NTP research report was published in October 2017. |
| Environmental influences on the epigenome: a scoping report<br><br>Study Scientists: Katie Pelch and Vickie Walker | NIEHS is interested in understanding the effects of the environment on epigenetic regulation of biological and pathological processes. Of the various epigenetic modifications, the alteration of DNA methylation patterns has been the most widely studied and highly funded modification to date. This evaluation will leverage newly developed text mining and machine learning tools to carry out scoping activities that will explore the evidence linking environmental exposures to health outcomes via genome-wide alterations in DNA methylation. The concept was reviewed at the June 2015 Board of Scientific Counselors meeting, and the evaluation is ongoing. |
| Shift work at night, light at night, and circadian disruption<br><br>Study Scientist: Windy Boyd | Circadian disruption occurs when endogenous circadian rhythms, which are daily and predictable variations in biological, physiological, and behavioral processes, are out of phase with the external environment or with each other. Through their work, lifestyle choices, or residences, people are subjected to interruptions in the natural light-dark cycles, leading to the potential for circadian disruption. This project is being undertaken in conjunction with an analysis by the Office of the Report on Carcinogens for cancer hazard evaluation. The concept was reviewed at the April 2014 Board of Scientific Counselors meeting, and a public workshop/webinar was held at NIEHS in March 2016 to obtain expert opinion to inform potential health hazard assessments. The workshop report was published in Science of the Total Environment in December 2017. With the Office of the Report on Carcinogens, activity is underway to finalize the protocol and execute the cancer hazard evaluation. |
| Neonicotinoid pesticides and adverse health outcomes<br><br>Study Scientist: Windy Boyd | Neonicotinoid pesticides are a class of chemicals that act as insecticides by exerting neurotoxic effects through irreversible binding to insect nicotinic acetylcholine receptors. Nicotinic acetylcholine receptors are also present in the nervous systems of mammals, raising concern that neonicotinoids might affect animals other than their insect targets, including humans. In Spring 2015, neonicotinoid pesticides were nominated to NTP for possible evaluation of noncancer health outcomes. In response, OHAT is conducting a scoping review to identify the extent of evidence available to understand human health effects of seven neonicotinoid pesticides (acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam). The protocol was posted in November 2017, and the evaluation is ongoing. |

| | |
|---|---|
| Parkinson's disease: associations with environmental exposures<br>Study Scientist: Windy Boyd | Parkinson's disease is a group of motor system disorders including tremor of the extremities, rigidity of the limbs and body, slowness of movement, and postural instability. Although some Parkinson's disease cases can be attributed to genetic factors, the causes of many cases remain unknown. Many studies report associations between environmental exposures and Parkinson's disease or related symptoms. OHAT is conducting two scoping reviews on this topic. The first project is a scoping review to systematically map the evidence of the associations between exposures to environmental chemicals considered broadly and Parkinson's disease. During scoping activities, hundreds of studies on the associations between exposure to the herbicide paraquat and Parkinson's disease were identified, making paraquat a candidate chemical for further systematic review. Therefore, a more detailed scoping review is being developed to characterize reported associations between paraquat exposure and Parkinson's disease. Both evaluations are ongoing. |
| Systematic reviews on potential health effects of fluoride<br>Study Scientist: Kyla Taylor | NTP is currently conducting a systematic review to evaluate potential neurobehavioral effects from exposure to fluoride during development that includes consideration of human epidemiology, additional experimental animal studies, and mechanistic data. This update to NTP's 2016 systematic review of published animal literature is examining neurobehavioral effects of exposure to fluoride during development and adulthood in rodents. The 2016 report concluded the evidence supporting adverse effects on learning and memory in animals exposed to fluoride in the diet or drinking water is low to moderate. The concept was approved at the December 2015 Board of Scientific Counselors meeting. The protocol was posted in July 2017, and the systematic review is ongoing. |

# Report on Carcinogens


## About the Report on Carcinogens

The Report on Carcinogens is a congressionally mandated listing of substances that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and to which a significant number of persons residing in the United States are exposed.



## Report Activities

A summary of activities the Office of the Report on Carcinogens conducted during FY 2017.

## Report Substances Selected for Evaluation

A list of substances the Office of the Report on Carcinogens selected for evaluation during FY 2017.

# About the Report on Carcinogens


The Report on Carcinogens is a congressionally mandated listing of substances that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens, and to which a significant number of persons residing in the United States are exposed [Section 301(b)(4) of the Public Health Service Act, 42 U.S.C. 241(b)(4)].

The Report is cumulative, consisting of newly reviewed substances in addition to those substances listed in previous editions. NTP follows an established four-part process when preparing the Report.

1. NTP selects nominations for Report evaluation.
2. The Office of Report on Carcinogens conducts cancer hazard evaluations on the nominated substances.
3. Draft Report monographs are released for public comment and peer review before finalization.
4. NTP submits the proposed listing of newly reviewed substances to the U.S. Department of Health and Human Services secretary for review, approval, and release to the public and congressional members.

Each substance listed in the Report has a profile, which contains the listing status determined by using established listing criteria, a summary of the cancer studies supporting the listing status, information on human exposure, and federal regulations to reduce exposure.

The Report is prepared by the Office of the Report on Carcinogens, under the direction of Ruth Lunn, Dr.P.H. Contract support for preparation of the Report in FY 2016 was provided by Integrated Laboratory Systems Inc. and ICF.

**Additional Links for the Report**

Report on Carcinogens

Report Activities in 2017

Report Candidate Substances

# Report Activities

The U.S. Department of Health and Human Services released the 14th Report on Carcinogens on November 3, 2016. This cumulative report contains 248 listings, of which 7 were newly reviewed. Report activities in FY 2017 primarily were related to identifying substances for review and preparing cancer hazard evaluations of several substances for review for future reports. The Office of the Report on Carcinogens at NIEHS prepared and released the draft monograph, Haloacetic Acids Found as Water Disinfection By-Products, for public comment. On July 24, 2017, an external panel of experts peer reviewed the draft monograph and agreed with NTP's preliminary recommendations to list six haloacetic acids in the next edition of the Report. The Office also developed a concept document proposing review of antimony trioxide for the Report. The concept was presented to the NTP Board of Scientific Counselors at their December 14–15, 2016 meeting.

Literature-based cancer hazard evaluations were initiated for:

- Antimony trioxide.
- Shift work at night, light at night, and circadian disruption.
- *Helicobacter pylori*: chronic infection.

For a list of ongoing evaluations, see Report Substances Selected for Evaluation.

# Office of Report on Carcinogens Staff Publications on Agents Recently Listed or Under Review

- Tumour virus epidemiology.
- Health consequences of electric lighting practices in the modern world: A report on the National Toxicology Program's workshop on shift work at night, artificial light at night, and circadian disruption.

**Additional Links for the Report on Carcinogens**

Report on Carcinogens

About Report on Carcinogens

Report Candidate Substances

# Report Substances Selected for Evaluation

| Substances<br>NTP Project Leader | Primary Uses/Exposures | Status |
|---|---|---|
| Antimony Trioxide<br>Amy Wang | Compound used mainly as a synergist for halogenated flame-retardants in plastics, rubber, and textiles, which are used in a diversity of plastics and other products. It also can be used as a catalyst in polyethylene terephthalate production, as an additive in glass manufacturing and in pigments, or as an additive in paints and ceramics. | Concept review: NTP Board of Scientific Counselors Meeting December 2016 |
| Goldenseal Root Powder (*Hydrastis canadensis*)<br>Office of Report on Carcinogens staff | Herbal remedy (botanical product) used to treat gastrointestinal disturbances; urinary disorders; hemorrhage; skin, mouth, and eye infections; and inflammation. | Concept review: NTP Board of Scientific Counselors Meeting April 2014 |
| Haloacetic Acids Found as Water Disinfection By-Products<br>Gloria Jahnke | Includes 13 individual haloacetic acids or a potential class or subclass of these haloacetic acids. People are exposed to these haloacetic acids by ingestion of chlorinated drinking water and by inhalation and dermal contact during bathing or showering or when using swimming pools and spas that use chlorine for disinfection. | Peer review of draft monograph:<br>July 2017 |
| *Helicobacter pylori* (*H. pylori*): Chronic Infection<br>Ruth Lunn | Gram-negative, multiflagellated bacterium that colonizes the stomach and causes peptic ulcer. Bacterium is spread by person-to-person contact, especially among family members. Routes of exposure include oral-oral, fecal-oral, and iatrogenic; exposure from contaminated water is also possible. Risks factors for infection include age, race, socioeconomic status such as crowded living conditions, and poor sanitation/hygiene. | Concept review: NTP Board of Scientific Counselors Meeting April 2016 |
| Shift Work at Night, Light at Night, and Circadian Disruption<br>Ruth Lunn | Unnatural (e.g., ill-timed) electrical light, especially light at night, may disrupt sleep and biological processes controlled by endogenous circadian clocks. People, who by virtue of the nature of their work, lifestyle choices, or residence, are subjected to exposure to unnatural light. Shift workers who work at night can experience an extreme type of exposure to light at night and changes in other activities, such as changes in daily activities, eating, sleeping, lifestyle factors, and social behavior. | Workshop: Shift Work at Night, Artificial Light at Night, and Circadian Disruption workshop<br>March 2016 |

**Additional Links for the Report on Carcinogens**

Report on Carcinogens

About Report on Carcinogens

Report Activities in 2017

# Partner Agency Research

## About NTP at NIEHS

Research activities in the Division of NTP at NIEHS are conducted through the several branches: Biomolecular Screening Branch, Cellular and Molecular Pathology Branch, NTP Laboratory, Program Operations Branch, and Toxicology Branch.

## NTP at NCTR

NCTR provides innovative technology, methods development, vital scientific training, and technical expertise to NTP.

## NTP at NIOSH

NIOSH research projects for NTP assess the effects of exposures to substances, following its mandate to protect worker health and safety.

# About NTP at NIEHS

Most NTP research testing and analysis activities are carried out at NIEHS. The following Division of NTP branches at NIEHS are actively involved in NTP research activities.

- Biomolecular Screening Branch, Richard S. Paules, Ph.D., acting chief.
- Cellular and Molecular Pathology Branch, Robert Sills, D.V.M., Ph.D., chief.
- NTP Laboratory, Michael DeVito, Ph.D., acting chief.
- Program Operations Branch, Michelle Hooth, Ph.D., chief.
- Toxicology Branch, Paul Foster, Ph.D., chief.

**NIEHS/NTP Staff**

## Biomolecular Screening

The Biomolecular Screening Branch develops and implements programs in medium- and high-throughput screening of environmental substances for rapid detection of biological activities of significance to toxicology. A focus is to develop analysis tools and approaches that integrate screening assessments with findings from traditional toxicology. The branch also administers the NTP High-Throughput Screening Initiative, which includes NTP's Tox21 activities. Tox21 emphasizes the

use of alternative assays for targeting the key pathways, molecular events, or processes linked to disease or injury, with the goal of incorporating the assays into a research and testing framework. An important priority for moving forward is to expand the biological coverage of the screening program and enhance the human relevance of alternative tests' findings. Key to this effort is the integration of high-throughput transcriptomic screening into Tox21 and other NTP studies. The development of the S1500+ gene set and its use in targeted sequencing approaches provides a new, cost-effective methodology for capturing broad biological responses to chemical exposures in a variety of in vitro and in vivo model systems, allowing for quantitative dose-response measurements and kinetic studies. Linking this high-throughput transcriptomic approach with novel organotypic cell culture model systems (i.e., models that behave like living tissue) allows for a more rapid and deeper investigation of biological responses for chemicals of concern and a better understanding of potential implications for human health.

Genetic and epigenetic differences between individuals in the human population have been proposed as major factors for determining individual susceptibility to environmental stressors. Safety assessments of environmental substances and drugs are currently conducted with a few commonly used animal models that have limited genetic diversity. Further, many layers of biological regulation can influence individual genetic susceptibility to chemical and drug toxicity. Animal models have inherent limitations for extrapolating results to human toxicity and disease. NTP is developing more sophisticated genetic analyses to make better use of current animal models while adopting biological systems that are more appropriate for modeling human toxicity and disease. The NTP Biomolecular Screening Branch conducts in-house projects aimed at understanding individual susceptibility.

Epigenetics involves the study of modifications to DNA and related cellular structures that affect gene expression and an organism's ability to adapt to the environment. In FY 2017, work continued on an epigenetic study of mouse strains, led by Alex Merrick, Ph.D., and Paul Wade, Ph.D., to examine DNA methylation and its possible role in the susceptibility of mice to develop liver tumors. Male and female C57BL/6N mice were crossed with C3H/HeN mice. Five tissue types—brain, liver, cardiac and skeletal muscle, brown and white fat, and epididymal sperm—from first-generation offspring were collected and flash frozen for DNA/RNA isolation and liver sequencing. Progress in FY 2017 included computational analysis of genomic methylation sites in relation to known genes and transcriptionally active regions in both parental strains and first-generation offspring. The relationships between DNA methylation, gene expression, and possible heredity in offspring are being determined, and the genomic variations in mouse strains, genders, and first-generation offspring are being catalogued. The epigenetic landscape in the two mouse strains and their offspring will be described to help interpret the contribution of differences in DNA methylation to differential susceptibility to hepatic malignancy. The data will be publicly released following completion of a manuscript. Additional studies in FY 2017 addressed the impact of sex hormone signaling on DNA methylation at a genome-wide level and the impact of DNA methylation at distal regulatory regions.

## NTP Laboratory

NTP Laboratory conducts in-house, agent-specific, targeted research on the development and application of modern toxicology and molecular biology tools. These tools are used to:

- Evaluate specific substances of concern to NTP.
- Identify issues of central importance to programs within NTP.
- Develop methods to advance the NTP mission.

NTP Laboratory also studies the developmental origins of adult diseases. NTP Laboratory projects for FY 2017 are listed below.

## NTP Laboratory Projects in FY 2017

| Project & Study Scientist | Project Summary |
|---|---|
| Development of in vitro models of metal carcinogenesis<br>Study Scientist: Erik Tokar | Use of in vitro cell transformation models (stem/progenitor and “mature” cells) of target-relevant cells to elucidate carcinogenic mechanisms and modes of action of metals (i.e., arsenic and cadmium). |
| In vitro evaluation of crumb rubber toxic effects<br>Study Scientist: Erik Tokar | Study of the modes of action and metabolomics involved in the toxic effects of crumb rubber on various prospective human target tissues. |
| Role of microRNAs in malignant transformation<br>Study Scientist: Erik Tokar | Study of genes involved in the epigenetics of malignant transformation using in vitro human model systems of carcinogenesis. MicroRNAs are thought to be a key epigenetic or posttranscriptional gene expression control mechanism. |
| Stem cells in toxicology: carcinogenesis, developmental toxicology, and developmental basis of adult disease<br>Study Scientist: Erik Tokar | Development of stem cell model systems (pluripotent, multipotent, progenitor) and methods for use in examining the role of these cells in carcinogenesis, evaluating developmental bases of adult disease, and assessing developmental toxicology. These studies will be used to help predict or categorize teratogens and developmental toxicants. |
| Evaluation of polycyclic aromatic hydrocarbon compounds using in vitro screens<br>Study Scientist: Erik Tokar | Application of in vitro assays to assess and categorize the biological effects of polycyclic aromatic hydrocarbon compounds. |
| Evaluation of the role of oxidative stress in the biological effects of glyphosate and its formulations<br>Study Scientist: Michael DeVito | Comparison of the effects of glyphosate to the effects of glyphosate formulations using measures of genotoxicity, oxidative stress, and cell viability. Comparison of the dose-response relationships among oxidative stress, genotoxicity, and cell viability. |
| Application of in vitro assays to evaluate botanicals<br>Study Scientist: Michael DeVito | Determination of whether in vitro assays and chemical analysis of botanicals can aid in selecting botanicals for in vivo testing. |
| Chemical-induced transcriptomic and metabolomic changes in vitro<br>Study Scientist: Michael DeVito | Evaluation of the transcriptomic and metabolomic changes in metabolically active cell lines with 24 chemicals that have been tested in vitro. |
| Incorporation of metabolism into high throughput screening assays<br>Study Scientist: Michael DeVito | Development of in vitro methods that incorporate xenobiotic metabolism. A manuscript is in development. |
| Utility of a five-day transcriptomic study in adult rats<br>Study Scientist: William Gwinn | Examination of the differences in the transcriptomic bone mineral density and adverse effect bone mineral density for 20 chemicals that have been tested in vitro at NTP. |

| Project & Study Scientist | Project Summary |
|---|---|
| PCB 11: Screening for biological and toxicological activity<br>Study Scientist: Michael DeVito | Comparison of the biological and toxicological activity of polychlorinated biphenyl (PCB) 11 to prototype PCBs in response to a nomination from EPA. |
| Metalloestrogens and uterine/breast response<br>Study Scientists: Darlene Dixon, Suzanne Fenton | Tests of the ability of reported metalloestrogens such as cadmium and arsenic to cause estrogen receptor stimulation in the uterus as a mode of action for cancer development. |
| The role of ER-alpha36 in endocrine disruption and its localization in fibroid cells<br>Study Scientist: Darlene Dixon | Evaluation of the role of endocrine disrupter alpha36 (ER-alpha36) in fibroid cells and the role of ER-alpha36 in the endocrine disrupting effects of environmental and industrial chemicals. |
| Literature-based evidence for environmental factors affecting the breast<br>Study Scientists: Suzanne Fenton, Jason Stanko, Vickie Walker | Review and categorization of the evidence in the literature on environmental influences on breast development, disease, and function. This work should lead to development of systematic reviews on related topics. |
| Effects of TBBPA on developmental and reproductive endpoints in Harlan SD rats<br>Study Scientists: Suzanne Fenton, Linda Birnbaum | Evaluation of the effects of TBBPA (tetrabromobisphenol A) following prenatal and early life exposure and determination of transcriptomic/metabolomic pathways involved in low-dose, hormone-driven responses. |
| Screening of perfluorinated compounds for effects in human and mouse cell-based assays<br>Study Scientists: Suzanne Fenton, Michael DeVito | Comparison of potencies and effect profiles of 40–75 perfluorinated compounds for their effects in cells known to be targets of PFOA and PFOS (perfluorooctanoic acid and perfluorooctane sulfonate, two perfluorinated compounds removed from the market due to reported health effects). |
| Toxicants and mammary gland development<br>Study Scientist: Suzanne Fenton | Determination of the effects of different toxicants, including atrazine and bisphenols, on mammary gland development in rats or mice. |
| Use of in vitro screens to evaluate potential obesogens<br>Study Scientist: Suzanne Fenton | Development of orthogonal assays to evaluate findings from Tox21 that identified potential obesogens. Mechanisms of action for select chemicals are being investigated. |
| Refinement of developmental neurotoxicology methods<br>Study Scientist: G. Jean Harry | Improvement of methods for assessing differential changes as a function of developmental exposures, including in vivo molecular phenotypes, cellular phenotypes, maternal/developmental inflammation, and behavioral assessments. |
| Method development to assess neuroinflammation<br>Study Scientist: G. Jean Harry | Examination of methods (from screening to mechanisms) for assessing in vitro and in vivo induction of inflammation in the nervous system following chemical exposures. |
| Evaluation of the developmental neurotoxicity of fluoride<br>Study Scientist: G. Jean Harry | Evaluation of fluoride developmental neurotoxicity in rats. The study has been completed, and a manuscript has been submitted. |

# NTP at NCTR

## About NTP at the National Center for Toxicological Research

NCTR provides innovative technology, methods development, vital scientific training, and technical expertise to NTP.

## NTP at NCTR: Interagency Agreement Projects

A list of projects funded by the NIEHS/NTP interagency agreement with FDA and conducted in FY 2017.

# About NTP at the National Center for Toxicological Research

## Research in Partnership with NCTR

The National Center for Toxicological Research (NCTR) partners with researchers from elsewhere in FDA, other government agencies, academia, and industry to provide innovative technology, methods development, vital scientific training, and technical expertise. The unique scientific expertise of NCTR is critical in supporting FDA product centers and their regulatory roles. NCTR research for NTP is funded by both voluntary allocations and an interagency agreement.

**NCTR/NTP Staff**

NCTR studies funded by voluntary allocations are listed below.

# Biochemical and Molecular Basis of Toxicology

| Project & Study Scientist | Project Summary |
|---|---|
| Physiologically based pharmacokinetic (PBPK) models for bisphenol A (BPA)<br><br>Study Scientist: Jeffrey Fisher | Creation of PBPK models for BPA in mouse, rat, and rhesus monkey for multiple life stages: adult; neonate; pregnant, mother and fetus; and lactating, mother and neonate. These PBPK models will be used to calculate internal measures of dose for both aglycone (i.e., active) and conjugated (i.e., inactive) forms of BPA. Human PBPK models for BPA (adult, neonate, pregnant mother and fetus, and lactating mother and infant) will be created using information obtained from the monkey, mouse, and rat models and from the limited human information published in the literature. The human suite of PBPK models will be used to extrapolate the internal doses of BPA associated with toxicity in laboratory animals to human doses. They will also be used to better characterize internal dosimetry of BPA. This simulation protocol will help reduce the uncertainty in assessment of health risks BPA poses to human populations. |
| Biologically based dose-response modeling for the thyroid axis in the fetus and neonate<br><br>Study Scientist: Jeffrey Fisher | (1) Creation of biologically based dose-response models for the hypothalamic-pituitary-thyroid axis in the developing rat and human as a function of iodide status.<br><br>(2) Interfacing of the models with physiologically based pharmacokinetic or toxicokinetic models for thyroid active chemicals with predicted conditions, such as iodide status and chemical exposure, for which brain thyroid hormone homeostasis cannot be maintained in the fetus and neonate.<br><br>(3) Use of the models to evaluate the possible influence of population exposures to thyroid active chemicals on fetal and neonatal thyroid status as a function of iodide intake. |
| Relationship between liver epigenetic phenotype and susceptibility to nonalcoholic steatohepatitis-induced (NASH) hepatocarcinogenesis in mice<br><br>Study Scientist: Igor Pogribny | (1) Determination of the role of epigenetic dysregulation in the etiology and pathogenesis of dietary NASH-induced hepatocarcinogenesis in mice.<br><br>(2) Determination of whether interstrain-specific susceptibility of mice to NASH-induced hepatocarcinogenesis is associated with differences in individual hepatic epigenetic phenotypes.<br><br>(3) Determination of the role of epigenetic dysregulation in the etiology and pathogenesis of NASH-induced hepatocarcinogenesis in mice induced by tamoxifen administration.<br><br>(4) Determination of whether aberrant epigenetic markers can be used as targets for preventing NASH- induced hepatocarcinogenesis in mice. |
| Sex differences in drug-induced QT prolongation and torsade de pointes: Establishing an in vitro model for high throughput screening and risk assessment of torsadogenic drugs<br><br>Study Scientist: Li Pang | (1) Establishment of the in vitro model and positive control.<br><br>(2) Evaluation of model sensitivity and specificity and tests of the possibility of high-throughput screening and ranking of QT-prolonging drugs for the risk of torsade de pointes. |

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| Mechanism of tumorigenic pyrrolizidine alkaloids and development of liquid chromatography-electrospray ionization/multistage mass spectrometry (LC-ESI/MS/MS) methodology for detection and quantification of pyrrolizidine alkaloids<br><br>Study Scientist: Peter Fu | (1) Validation of the proposed mechanism by which pyrrolizidine alkaloids induce tumors in rodents.<br><br>(2) Development of an LC-ES/MS/MS method for detecting and quantifying dehaloperoxidase-derived DNA adducts in rodents.<br><br>(3) Development of an LC-ES/MS/MS method for detecting and quantifying genotoxic pyrrolizidine alkaloids in herbal plants and herbal dietary supplements.<br><br>(4) Development of an LC-ES/MS/MS method for detecting and quantifying dehaloperoxidase-derived hemoglobin adducts in rodents. |
| Human biomonitoring for bisphenol A (BPA)<br><br>Study Scientist: Daniel Doerge | (1) Development and implementation of a sensitive and selective analytical methodology to measure BPA in human blood and urine.<br><br>(2) Integration of animal exposure data and human biomonitoring data into a PBPK model for BPA. |
| Evaluation of the effects of black cohosh on risedronate efficacy in perimenopausal rat model<br><br>Study Scientist: Amy Inselman | Determination of the effects of risedronate and black cohosh (alone or combined) on bone density, bone turnover, and bone histology in a postmenopausal rat model. |
| Development and evaluation of a novel in vitro epigenomic screening model system for the hazard identification of FDA-regulated products<br><br>Study Scientist: Igor Pogribny | (1) Determination of the dose-dependent, in vitro genetic and epigenetic effects of compounds FDA regulates.<br><br>(2) Characterization of the specific epigenetic changes induced in vitro by genotoxic and nongenotoxic compounds.<br><br>(3) Characterization of the specific genetic and epigenetic effects of compounds FDA regulates using an in vitro three-dimensional organotypic liver culture model system. |
| Developing methods for the analysis of brominated vegetable oils and derivatives<br><br>Study Scientist: Gonçalo Gamboa da Costa | Development of methods for analyzing the food additive, brominated vegetable oil, in rat feed and rat tissues. |
| Identification of mechanistic biomarkers of pyrrolizidine alkaloid (PA)-induced hepatocarcinogenesis<br><br>Study Scientist: William Tolleson | Use of high-throughput profiling approaches to identify microRNAs that regulate genes involved in PA carcinogenicity in hepatic cell systems and investigation of the functions of microRNAs by bioinformatics tools and in vitro functional assays. These results will identify microRNA species for use as biomarkers for PA-induced carcinogenicity, with added benefits derived from mechanistic knowledge of how these microRNAs might function in the biological effects of PAs. The discovery and characterization of microRNAs associated with the hepatocarcinogenic activity of PAs will benefit food safety and human health by providing simple tools for assessing exposure to foodborne toxins. |

## Neurotoxicology

| Project & Study Scientist | Project Summary |
|---|---|
| Assessment of gaseous anesthetics in the developing nonhuman primate<br><br>Study Scientist: John Talpos | (1) Determination of the dose-response effects of gaseous anesthetics nitrous oxide and isoflurane (individual or combined) on neuronal cell death in the developing nonhuman primate using magnetic resonance imaging (MRI) and positron emission tomography (MicroPET).<br><br>(2) Determination of the effects of dose and duration of gaseous anesthetics on nonhuman primate long-term behavior and pathology using MRI and MicroPET.<br><br>(3) Evaluation of antioxidants in the amelioration of toxicity associated with gaseous anesthetics. |
| Developmental neurotoxicity assessment of N-methyl-D-aspartate (NMDA) receptor antagonists in zebrafish<br><br>Study Scientist: Jyotshnabala Kanungo | (1) Study of wildtype zebrafish embryos exposed to NMDA receptor antagonists (MK-801, dextromethorphan, ketamine, and sevoflurane) to assess their effects on Rohon-Beard sensory neurons. The effects on the primary and secondary motor neurons and their axons are being assessed using hb9:GFP transgenic embryos. Postexposure washout experiments are being pursued to determine the effects of these drugs on the nervous system.<br><br>(2) Determination of estradiol-17β levels in control and treated embryos and quantification of changes in gene expression for the two CYP aromatases/estrogen synthases (brain aromatase cyp19a1b and gonadal aromatase cyp19a1a) using quantitative polymerase chain reaction (qPCR).<br><br>(3) Assessment of phenotype-based cell signaling mechanisms, such as MAPK (mitogen-activated protein kinases) and neuron development-specific gene expression.<br><br>(4) Examination of reversal of noted adverse effects of these compounds on neurons, particularly by treatment with acetyl L-carnitine. |
| Toxicity assessment of graphene sheets using primary striatal neurons<br><br>Study Scientist: Syed Ali | (1) Evaluation of the toxicity of graphene sheets using in vitro primary cultures of embryonic day 14 primary rat striatal neurons.<br><br>(2) Determination of pathways involved in graphene toxicity using embryonic day 14 primary rat striatal neurons. |
| Identification of protein biomarkers for neurotoxicity assessments using a high-throughput antibody microarray approach<br><br>Study Scientist: Qiang Gu | (1) Examination of proteomic changes at the expression and phosphorylation levels using five established in vivo models of neurotoxicity.<br><br>(2) Identification of common changes in protein expression and phosphorylation status in these animal model systems.<br><br>(3) Confirmation of the observed alterations in protein expression and phosphorylation status by independent methods.<br><br>(4) Application of the proteomic findings to a global ischemic animal model to verify the utility of protein biomarkers for use in neurotoxicity assessments. |

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| Effects of developmental sevoflurane exposure and pretreatment with acetyl-L-carnitine on complex brain function in rats<br>Study Scientist: John Chelonis | (1) Examination of the effects of early developmental sevoflurane exposure on neurodegeneration and complex operant learning.<br>(2) Determination of whether pretreatment with acetyl-L-carnitine can attenuate impairments in these measures.<br>(3) Examination of the time course of acetyl-L-carnitine pretreatment on sevoflurane-induced neuroapoptosis. |
| Rat blood-brain-barrier-on-a-chip model to study traumatic brain injury<br>Study Scientist: Syed Ali | (1) Use of soft lithograph and microfabrication techniques to engineer a multilayered blood-brain-barrier-on-a-chip model that can be subjected to different magnitudes and durations of mechanical stress that mimic mild and repetitive traumatic brain injury.<br>(2) Characterization of the effects of traumatic brain injury on blood-brain-barrier integrity using the chip model. |
| High-throughput neurotoxicity screening of metallic nanoparticles: In vitro and in vivo imaging<br>Study Scientist: Syed Imam | Assessment of the utility of high-throughput neurotoxicity screening of metallic nanoparticles for detecting neurochemical and neurophysiological alterations in vitro for use in developing reference standards for metallic nanoparticles. Once developed and validated, these techniques can be optimized for analyzing other FDA-regulated nanomaterials. |

## Nanotoxicology

| Project & Study Scientist | Project Summary |
|---|---|
| Proteomic assessment of the cytotoxic effects of nanoparticles on the blood-brain barrier<br>Study Scientist: Qiang Gu | Use of proteomic approaches to quantify alterations in expression and phosphorylation of proteins involved in apoptosis, inflammation, oxidative stress, and tumorigenesis signaling pathways in blood-brain barrier cells following exposure to nanoparticles. The long-term goal is to establish proteomic parameters for toxicity of nanoparticles. |
| Complement assays for the detection of immune-sensitizing activity of nanomaterials<br>Study Scientist: Julian Leakey | (1) Establishment of two complement assays for routine evaluation of immune-sensitizing activity of nanomaterials.<br>(2) Validation of the assays using nanoparticles with known immunoreactivity.<br>(3) Determination of the immune-sensitizing activity of novel nanomaterials. |
| Physiologically based pharmacokinetic (PBPK) modeling of nanomedicine: Building clinically relevant standards for FDA-regulated nanoparticulate drug products<br>Study Scientist: Julian Leakey | (1) Determination of in vivo liposomal doxorubicin release kinetics in individual tissues and the blood stream using PBPK modeling.<br>(2) Establishment of quantitative physicochemical property (liposomal size and content of ammonium sulfate) biodistribution relationships of liposomal doxorubicin products by PBPK modeling.<br>(3) Extrapolation of the PBPK model to rats and humans. A whole-body PBPK model is being developed to describe and simulate the biodistribution of liposomal vesicles and doxorubicin. |

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| Assessment of size- and shape-dependent toxicity of silver (Ag) nanoparticles as measured by changes in the permeability at the gastrointestinal surface<br><br>Study Scientist: Sangeeta Khare | (1) Determination of the effect of nanomaterials on the permeability of intestinal epithelial cells in vitro and ileal mucosa ex vivo.<br><br>(2) Investigation of various cellular components involved in the uptake of nanoparticles in intestine, their accumulation in various cell types, and the effect of nanoparticles on the intestinal microbiome.<br><br>(3) Measurement of the toxicity of silver nanoparticles using changes in the expression of genes involved in the epithelial integrity of polarized epithelial cells and ileal mucosa. |
| In vitro genotoxicity of graphene-family nanomaterials using FDA-recommended short-term genetic toxicity test battery<br><br>Study Scientist: Nan Mei | (1) Determination of the genotoxicity of graphene and derivatives in standard regulatory test battery assays.<br><br>(2) Determination of whether any mutagenicity in mouse lymphoma cells is due to loss of heterozygosity in chromosome 11.<br><br>(3) Investigation of whether genotoxic and mutagenic responses are mediated through oxidative pathways.<br><br>(4) Establishment of the genotoxic and mutagenic mode of action using gene expression arrays. |
| Graphene-induced toxicity on the population of intestinal microbiota and gut-associated immune response<br><br>Study Scientist: Sangeeta Khare | Evaluation of the effects of graphene on gastrointestinal homeostasis by determining graphene derivative effects on intestinal bacterial cultures, polarized intestinal epithelial cells, intestinal commensal bacteria in vivo, and gastrointestinal immune responses in vivo. |
| NCTR/Office of Regulatory Affairs (ORA) Nanotechnology Core Facility<br><br>Study Scientist: Anil Kumar Patri | (1) Provision of the expertise and equipment for characterizing nanomaterials used in toxicology studies and for detecting nanomaterials in in vitro and in vivo derived samples.<br><br>(2) Serving as a resource for U.S. agencies for the design of toxicology studies and generation of standards for analytical methods. |
| Assessment of whether engineered Ag nanomaterials (Ag-ENMs) varying by size and coatings behave differently from bulk Ag in their ability to induce genetic damage<br><br>Study Scientist: Tao Chen | (1) Evaluation of whether the Ames test and mouse lymphoma assay, in addition to the in vitro micronucleus assay, are suitable for detecting the genotoxicity of titanium dioxide ($TiO_2$) nanoparticles, a known rodent carcinogen.<br><br>(2) Investigation of Ag-ENPs of various sizes and compare the results to those obtained using bulk Ag. |
| Determination of cytotoxicity and genotoxicity of nanomaterials of interest to the FDA and their mechanism of action<br><br>Study Scientist: Peter Fu | (1) Development of a set of cell-free and cell-based in vitro tests that can be used to rapidly identify nanomaterials of interest to the FDA that elicit oxidative damage.<br><br>(2) Determination of whether, in the presence of nano-metal materials, endogenous and dietary antioxidants can display pro-oxidative activity. |

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| Assessing epigenetic effects of nanoparticles in human cells<br><br>Study Scientist: George Hammons | (1) Determination of the effect of two types of nanoparticles, silver and titanium dioxide, at various particle sizes, surface coatings, dosages, and durations of exposure on global methylation and genome-wide DNA methylation using array profiling in four types of human cells (liver, lung, skin, and colorectal).<br><br>(2) Determination of the effect of these nanoparticles on the pattern of global histone modifications and on genome-wide profiles of histone modifications in the four types of human cells. The analysis includes comparisons with disease-associated histone modifications.<br><br>(3) Correlation of the nanoparticle effect on DNA methylation with its effect on DNA methyltransferase expression.<br><br>(4) Correlation of the nanoparticle effect on global histone modifications with its effect on expression of histone-modifying enzymes as potential underlying mechanisms of the alteration in DNA methylation or histone modification patterns. |
| Immunotoxicity assessment of nanomaterials using human immune cell based biomarkers of innate immunity<br><br>Study Scientist: Wei Ding | Assessment of the immunotoxicity of different categories of nanoparticles using biomarkers of innate immunity measured in vitro in human immune cells (monocytes, human peripheral blood mononuclear cells). |
| An assessment of the interactions of nanoscale ($TiO_2$ and zinc oxide) materials used in sunscreens on the skin microbiome<br><br>Study Scientist: Tao Chen | (1) Examination of human skin microbiota cell viability in the presence of nanoscale materials in cosmetics.<br><br>(2) Determination of the effect of nanomaterials in cosmetics on human skin microbial ecology.<br><br>(3) Demonstration of the mechanisms of toxicity of nanoscale materials in cosmetics to skin microbiota using the human skin tissue model EpiDerm and reverse transcription polymerase chain reaction (RT-PCR) and whole genome microarray technologies.<br><br>(4) Elucidation of the dose-response relationship of nanoscale materials in cosmetics on skin bacterial cell toxicity.<br><br>(5) Assessment of the potential health risk of human skin exposure to nanomaterials in cosmetics. |
| Evaluation of the migration and toxic potential of Ag nanoparticles in feminine hygiene products to vaginal tissue: In vivo rodent and in vitro 3D mucosal models<br><br>Study Scientist: Anil Patri | (1) Use of established qualitative methods to characterize different species of nanoscale Ag contained in five types of dry and five types of liquid feminine hygiene products.<br><br>(2) Evaluation of the migration/uptake and toxicity of Ag nanoparticles and ions used in feminine hygiene products using a human cell-based in vitro three-dimensional culture model that has many of the structural and functional features of the human vaginal mucosal layer.<br><br>(3) Evaluation of the effects of Ag nanoparticles and ions contained in feminine hygiene products on human vaginal microbiota using culture techniques and semiquantitative molecular methods. |

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| Interaction of nanoparticles with gastrointestinal tract<br>Study Scientist: Sangeeta Khare | (1) Determination of the effect of nanomaterials on the permeability of epithelial cells and establishment of immune correlates.<br>(2) Delineation of the interaction of nanomaterials with gastrointestinal tract and gut-associated microbiota using an ex-vivo model (intestinal explants).<br>(3) Establishment of the effect of nanoparticles on the developmental stage of the intestine and assessment of the biodistribution of nanoparticles using the zebrafish model. |
| The effect of nanomaterials used in dentistry on biofilm formation and the oral microbiota<br>Study Scientist: John Sutherland | (1) Comparison of the relative efficacy of FDA-regulated nanomaterials used in dentistry for inhibition of bacterial adhesion to surfaces and biofilm formation.<br>(2) Evaluation of the effect of nanomaterials on growth and antimicrobial susceptibility profiles of typical species from the oral microbiota. |
| Mechanistic toxicological evaluation of engineered nanomaterials using a human stem cell model<br>Study Scientist: Anil Patri | (1) Establishment of the human stem cell model for nanotoxicity testing.<br>(2) Exploitation of the preliminary observation that titanium dioxide inhibits mesenchymal stem cell differentiation into adipocytes while other nanomaterials have no effect on the cells.<br>(3) Establishment of a novel sensitive model for nanotoxicity testing and provision of that information to FDA regulators on effects of titanium dioxide and other nanomaterials used in food, drugs, cosmetics, and medical products. |

## Bioassay and Biomarker Development and Evaluation

| Project & Study Scientist | Project Summary |
|---|---|
| Development of cancer-relevant biomarkers for identification of potential carcinogens: Research to understand the normal background frequencies in rats<br>Study Scientist: Page McKinzie | (1) Understanding of the distribution and range of spontaneous oncogene mutant frequencies in the major organs of rats and mice.<br>(2) Provision of important basic information for the validation of these oncogene mutant frequencies as biomarkers of chemically induced carcinogenesis. |
| Validation of a newly developed transgenic, hairless, albino mouse<br>Study Scientist: Manju Manjanatha | Evaluation of a newly developed transgenic, hairless, albino mouse bearing a gpt-delta reporter construct (THA) for responsiveness of the construct (gpt and spi- red/gam genes) to UVB (ultraviolet B radiation). The animal will be used to examine kinetics of induction of UVB-induced mutations in a reporter construct in the dermis and epidermis and to correlate activity with UVB induction of skin tumors. |
| Study of translational biomarkers for drug-induced liver injury with next-generation sequencing<br>Study Scientist: Yuping Wang | Conduct of a comprehensive survey of microRNAs using the next generation sequencing technology. Findings will elucidate the molecular pathways and processes modulated by RNAs (including messenger RNAs, microRNAs, and other noncoding RNAs) and their importance in drug-induced liver injury risk and phenotypes. |

| Project & Study Scientist | Project Summary |
|---|---|
| A comprehensive characterization of induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) models for drug-induced arrhythmia using high-throughput screening assays<br>Study Scientist: Li Pang | (1) Development of standard baseline criteria for high-throughput readouts of drug-induced arrhythmia in human iPSC-CMs from different suppliers.<br>(2) Assessment of individual variance and possible sex differences in drug-induced cardiotoxic responses across a panel of nongenetically modified iPSC lines. |
| Validating the rat Pig-a assay for regulatory use: Determining the molecular basis of mutants detected in the rat Pig-a gene mutation assay<br>Study Scientist: Vasily Dobrovolsky | Development of a method that could routinely identify Pig-a mutations in individual Pig-a mutant phenotype cells. |
| Developing in vitro approaches to assess drug-induced liver toxicity<br>Study Scientist: Lei Guo | Development and utilization of in vitro assays for assessing drug-induced liver toxicity by evaluating cytotoxicity and quantifying representative endpoints for assessing clinical-related outcomes such as apoptosis/necrosis, steatosis, and cholestasis. |
| Evaluation of microRNAs in blood and urine for detection of chemical-induced carcinogenicity<br>Study Scientist: Tao Chen | (1) Determination of microRNAs in blood and carcinogenic target tissues that respond to carcinogen exposures and the best time for sampling of their expression after treatments in rats.<br>(2) Determination of microRNA profiles from the blood and target tissue samples of rats treated with different mode-of-action carcinogens, such as alkylating agents, aneugens, clastogens, and nongenotoxic carcinogens at the appropriate sampling time.<br>(3) Determination of the functions and pathways of the dysregulated microRNAs by the carcinogen treatments and examine whether the microRNA changes can be anchored to the carcinogens with the known mode-of-actions and whether the changes in blood are related to those in the target tissues.<br>(4) Establishment of specific microRNA biomarkers in blood for assessing different types of carcinogens. |
| Development and characterization of a diet-induced obesity model using B6C3F1 mouse for evaluation of drug toxicity in obesity<br>Study Scientist: Vijayalakshmi Varma | Development of a B6C3F1 mouse model of obesity to investigate the impact of obesity on anthracycline-induced cardiotoxicity and the model's suitability to investigate other potential drug-induced toxicities under conditions of obesity. |
| Development of advanced safety assessments of FDA-regulated products using high-throughput and high-content quantitative approaches in cultured human cells to evaluate genotoxicity<br>Study Scientist: Carol Guo | Establishment and demonstration of the feasibility of novel high-throughput and high-content in vitro genotoxicity assays conducted using human liver cells in conjunction with quantitative dose-response approaches for assessing and distinguishing the genotoxicity of FDA-regulated products. |
| Enhance the prediction of potential endocrine activity of chemicals by integrating multiple endpoints data<br>Study Scientist: Huixiao Hong | (1) Augmentation of different endocrine-related endpoint data and development of prediction models for screening chemicals with endocrine activity potential by integrating the augmented multiple types of endocrine-related endpoint data.<br>(2) Building of an androgenic activity database and construction of integration-based prediction models. |

| Project & Study Scientist | Project Summary |
|---|---|
| Evaluation of an in vitro testis organ system as an alternative model for male reproductive toxicology<br>Study Scientist: Noriko Nakamura | Evaluation of the in vitro testis organ system as an alternative model to assess male reproductive toxicology and establishment of a standardized protocol for the assay. |

## Computational Toxicology

| Project & Study Scientist | Project Summary |
|---|---|
| Improving methods and algorithms for enhancing 3D-QSDAR<br>Study Scientist: Svetoslav Slavov | Testing of the feasibility and implementation of software code for enhancements to the three-dimensional quantitative spectral data-activity relationship (3D-QSDAR) technique and demonstration of the potential beneficial effect on the performance of 3D-QSDAR models for various data sets and endpoints. |
| Computational toxicology for safety and risk assessment<br>Study Scientist: Jeffery Fisher | Assistance to other FDA Centers and research organizations outside of FDA with their requests for support from staff scientists within NCTR and other scientists on safety and risk assessment issues of interest to FDA. |
| Pilot study to examine a population-based computational framework for assessing xenobiotic disposition and interaction effects in pregnant women<br>Study Scientist: Annie Lumen | (1) Demonstration of a proof of concept for using emerging computational techniques in understanding pregnancy-related alterations in drug pharmacokinetics.<br>(2) Assistance in developing recommendations for dose adjustments and drug labeling in the pregnant population, thus promoting women's health during this crucial period. |
| Hepatoxicity of herbal/dietary supplements<br>Study Scientist: Weida Tong | Assembly of a comprehensive list of herbal and dietary supplements that have potential to cause drug-induced liver injury in humans into a web-based database that can be used for reference in regulatory processes when hepatotoxicity issues arise. |

# NTP at NCTR: Interagency Agreement Projects

NCTR research for NTP is funded by voluntary allocations and an interagency agreement. Below are FY 2017 projects funded through an NIEHS/NTP interagency agreement with FDA.

## Food Additives and Contaminants

| Project & Study Scientist | Project Summary |
|---|---|
| Two-year chronic toxicology study of BPA in rats<br>Study Scientist: Barry Delclos | Characterization of the long-term toxicity of orally administered BPA (bisphenol A), including developmental exposure, in NCTR Sprague Dawley rats over a broad dose range. Animals generated in this study are being assigned to separate protocols for assessment of a range of molecular, morphological, and functional endpoints to determine if these endpoints are predictive of long-term toxic effects or reveal potential effects undetected by standard toxicological evaluations. |
| Evaluation of molecular, morphological, and functional endpoints in rats treated with BPA<br>Study Scientist: Barry Delclos | Evaluation of a range of molecular, morphological, and functional endpoints in rats dosed orally with a wide range of BPA doses in a chronic toxicology study. The endpoints were selected based on reports from previous animal toxicology or human epidemiology studies, suggesting they are affected by BPA exposure. Assessments are being conducted at various ages (postnatal days 1, 21, and 90 and 6 and 12 months) to determine if any effects observed are predictive of long-term effects evaluated in the companion chronic toxicology study, or if they reveal potential effects undetected by standard toxicological evaluations. |
| Combined nephrotoxicity of melamine and cyanuric acid in rats (recovery study)<br>Study Scientist: Gonçalo Gamboa da Costa | Assessment of the degree of functional and histological recovery after 30- and 90-day recovery periods in rats orally co-exposed with melamine and cyanuric acid for 90 days. |
| Comparison of the dose-response and temporal dynamics of traditional and novel biomarkers of nephrotoxicity upon a combined exposure to melamine and cyanuric acid in rats<br>Study Scientist: Luisa Camacho | (1) Comparison of the dose-response and temporal dynamics of circulating microRNAs, blood urea nitrogen, and serum creatinine in rats co-exposed to melamine and cyanuric acid over a 90-day treatment period and a subsequent 90-day recovery period.<br>(2) Comparison of the dose-response relationships of the kidney gene expression level of biomarkers of nephrotoxicity and kidney histopathology in rats co-exposed to melamine and cyanuric acid for 90 days and upon a 90-day recovery period. |
| Role of perinatal development on toxicokinetics of inorganic arsenic<br>Study Scientist: Daniel Doerge | Determination of serum pharmacokinetics and metabolism of low-dose inorganic arsenic in adult female CD-1 mice, Sprague Dawley rats, and rhesus monkeys. |
| Evaluation of brominated vegetable oil in rats<br>Study Scientist: Gonçalo Gamboa da Costa | (1) Assessment of the dose-response relationships of a 90-day dietary exposure to brominated vegetable oil in Sprague-Dawley rats.<br>(2) Evaluation of the bioaccumulation and clearance of inorganic and organic bromine in organs and tissues of Sprague-Dawley rats upon dietary exposure to brominated vegetable oil. |
| Developmental neurotoxicity evaluation of inorganic arsenic exposure in rats | (1) Determination of appropriate doses and survivability for direct oral inorganic arsenic exposure in neonatal Sprague-Dawley rats. |

| Project & Study Scientist | Project Summary |
|---|---|
| Study Scientist: Sherry Ferguson | (2) Development and refinement of techniques for future, more comprehensive studies.<br>(3) Determination of the early neurobehavioral toxicology of inorganic arsenic exposure on two preweaning behaviors and developmental milestones. |

## Dermal Toxicology Program

| Project & Study Scientist | Project Summary |
|---|---|
| Two-year dermal carcinogenicity of triclosan in B6C3F1 mice<br>Study Scientist: Jia-Long Fang | Determination of the toxicity and carcinogenicity of topically applied triclosan in mice. |

## Dietary Supplement Program

| Project & Study Scientist | Project Summary |
|---|---|
| Thirteen-week dosed water study to determine the potential toxicity of aloin in the cecum and large intestine of F344 rats<br>Study Scientist: Mary Boudreau | Evaluation of whether drinking water administration of aloin-A and aloin-B to F344 rats exerts similar effects in the rat large intestine when administered at concentrations similar to those in previous NCTR studies on *Aloe vera* whole leaf extract. |
| Effects of fibrinolytic enzymes nattokinase and lumbrokinase alone or in combination with aspirin in blood parameters<br>Study Scientist: Luisa Camacho | Evaluation in an animal model of the effects of nattokinase and lumbrokinase on blood parameters and assessment of their effects in combination with pharmacological doses of aspirin. |

## Drugs Program

| Project & Study Scientist | Project Summary |
|---|---|
| Toxicokinetic profile and toxicity of high-molecular-weight polyethylene glycols in rats<br>Study Scientist: Jia-Long Fang | (1) Evaluation of the toxicokinetic profile of high-molecular-weight polyethylene glycols in Sprague-Dawley rats given a single dose of the substances via subcutaneous injection.<br>(2) Evaluation of the bioaccumulation of high-molecular-weight polyethylene glycols in organs/tissues of rats upon repeated subcutaneous injection for 24 weeks.<br>(3) Assessment of the toxicities resulting from the bioaccumulation of the substances. |

## Enhancing Toxicology Program

| Project & Study Scientist | Project Summary |
|---|---|
| NTP capability building for microbiome assessment on toxicology studies: Assessing the role that the microbiome may play in the toxicity of xenobiotics<br>Study Scientist: Carl Cerniglia | Addressing critical knowledge gaps in the microbiome field using the latest advances in microbiome analysis through in vitro, in vivo, and ex vivo models in toxicity testing risk assessments. |

| Project & Study Scientist | Project Summary |
|---|---|
| Developing an in vitro system to evaluate the disease-related toxic effects of inhaled test agents in human airway tissue models<br><br>Study Scientist: Xuefei Cao | (1) Development of exposure and dosimetry methods for exposing human air-lung interface airway cultures to aerosolized test agents.<br><br>(2) Use of previously developed disease-related endpoints and air-lung interface culture exposure methods to evaluate the respiratory toxicity of two known airway toxicants, two presumed nontoxicants, and one compound of current interest. |
| Evaluation of genotoxicity and epigenetic modification of black cohosh extract (BCE) using the modified comet assay<br><br>Study Scientist: Manju Manjanatha | (1) Performance of alkaline single-cell gel electrophoresis (Comet) assays to detect DNA single- and double-strand breaks using several human cell lines.<br><br>(2) Performance of modified Comet assays using the addition of uracil-DNA glycosylase to evaluate the potential underlying mechanism(s) of BCE-associated genotoxicity.<br><br>(3) Performance of recently established modified Comet assays using DNA restriction enzyme, McrBC, which specifically recognizes DNA sites of the form 5'-R(m)C-3' and cuts DNA at methylated Cs for evaluating methylation modification by BCE. |

# NTP at NIOSH

## About NTP at NIOSH

NIOSH research projects for NTP assess the effects of exposures to substances following its mandate to protect workers' health and safety.

## NTP at NIOSH: Immunotoxicology Research

A list of studies to evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases.

## NTP at NIOSH: Occupationally Relevant Exposures

A summary and list of projects to identify and assess worker exposures in FY 2017.

# About NTP at NIOSH

In accordance with its mandate to protect worker health and safety, the National Institute for Occupational Safety and Health (NIOSH) carries out research projects with NTP through an interagency agreement with NIEHS to assess the effects of exposure to substances. Setting priorities in occupational toxicological research is based on several sources of information NIOSH develops and maintains. Sources include health hazard evaluations, industry-wide studies, gaps in knowledge identified while developing criteria for recommended standards or criteria documents, current intelligence bulletins, hazard reviews and alerts, other technical reports, and information profiles on chemical hazards. NIOSH research projects with NTP are funded by voluntary allocations and an interagency agreement focused on comprehensive assessment of occupationally relevant exposures and immunotoxicology research.

**NIOSH Staff: Health Effects Laboratory Division; Education and Information Division; Division of Applied Research and Technology and Division of Surveillance, Hazard Evaluations, and Field Studies**

NIOSH/NTP projects in FY 2017 funded through voluntary allocations are listed below.

## Biomonitoring, Biomarker Development, and Health Assessment

| Project & Study Scientist | Project Summary |
|---|---|
| Exposure assessment research and support<br><br>Study Scientist: John Snawder | Support of multiple branch and interdivisional projects through (1) managing and planning field sample collection, (2) developing new classical and immunochemical biomonitoring methods, and (3) validating and adapting existing methods. Biological monitoring can assess exposure by analyzing acute and latent metabolites in various biological media. This project will develop low-cost, rapid immunochemical and analytical chemistry biomonitoring methods to be used to identify exposures and evaluate potential interventions. Concurrent with development of exposure assessment methods, this project will identify and develop new multiplex immunochemical methods to evaluate biomarkers of occupational illness or subclinical signs of occupational illness. |
| Ultraviolet native fluorescence-based monitor for workplace exposures<br><br>Study Scientist: John Snawder | Development and evaluation of a readily adaptable, next-generation, direct-reading personal monitor for use in measuring worker exposure to a wide variety of chemicals, including naphthalene and components of asphalt fume. The development of personal monitors for volatile and semivolatile workplace chemicals will be helpful in rapidly assessing chemical exposure and will result in more realistic occupational exposure assessments. These assessments will allow for rapid interventions leading to reduced worker exposures and helping prevent occupational illness and disease. |

| Project & Study Scientist | Project Summary |
|---|---|
| Evaluation of welding fumes as a lung carcinogen in mice exposed by inhalation<br>Study Scientist: Patti Erdely | Investigation of both carcinogenic metal-containing and non-carcinogenic metal-containing welding fumes as lung carcinogens using a two-stage initiation-promotion mouse model. The findings will establish if welding fume inhalation at relevant occupational exposure levels increases lung tumorigenesis. The project also is generating valuable data regarding the carcinogenic potential of fumes from different types of welding processes that contain or do not contain carcinogenic metals. In addition, the project is providing information on which metal oxide components of the welding fume have the greatest carcinogenic potency. Thus far, the results of this project have contributed to the reevaluation of welding fumes by the International Agency for Research on Cancer in March 2017. |
| Systematic assessment of cobalt oxide (CoO) and lanthanum oxide ($La_2O_3$) in pulmonary disease<br>Study Scientist: Yong Qian | Investigation of cobalt oxide and lanthanum oxide nanoparticle-induced pulmonary injury in vivo and cellular toxicity in vitro. This project will reveal the toxicological modes of action for cobalt oxide and lanthanum oxide nanoparticles. Metal oxide nanoparticles are an important class of engineered nanomaterials with broad application in many industrial products. Concerns over potential metal oxide nanoparticle-induced toxicity have emerged, particularly due to the propensity of these nanoparticles to induce oxygen radicals and oxidative stress. Results obtained from this study will lead to development of methods for early detection and interventions of cobalt oxide and lanthanum oxide-induced pulmonary diseases, particularly fibrosis, in humans. |
| Industry-wide studies of workers exposed to carbon nanotubes and nanofibers<br>Study Scientist: Mary Schubauer-Berigan | Collection of exposure data and exposure factors from participating pilot-scale or full-scale manufacturers or users of single-walled carbon nanotubes (SWCNTs) or multiwalled carbon nanotubes and carbon nanofibers. A study of biomarkers for early pulmonary, cardiovascular, and carcinogenic effects was carried out among workers at these facilities. The creation of a predictive model using the collected exposure factors will allow for the estimation of exposure for future registry and cohort studies. |
| Mortality, cancer incidence, and biomarker studies<br>Study Scientist: James Yiin | Elucidation of exposure-outcome associations, especially dose-response relationships, for risk assessment and to examine relationships between biomarkers of exposure, susceptibility, and oncogene expression and determine health effects. |

## Environmental Monitoring

| Project & Study Scientist | Project Summary |
|---|---|
| Analytical research and development infrastructure<br>Study Scientist: Robert Streicher | Support of administrative needs and analytical instrumentation repair and maintenance for Chemical Exposure and Monitoring Branch chemists conducting research on sampling and developing analytical methods for workplace chemicals. Development, evaluation, validation, and use of methods for evaluating bisphenol A, manganese speciation, flame retardants, and other chemicals are part of the NIOSH/NTP exposure assessment interagency agreement. |

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| Diacetyl exposure assessment<br><br>Study Scientist: Robert Streicher | Development and evaluation of sampling and analytical methods for diacetyl and other higher molecular-weight alpha dicarbonyl flavoring compounds to enable accurate exposure assessment and evaluation of the effectiveness of control technology. Two sampling and analysis methods are being investigated for measurement of specific flavoring compounds, most notably diacetyl and 2,3-pentanedione. One method measures alpha dicarbonyl compounds present as vapor; the other measures the compounds in airborne particles and bulk powders. A modification to improve a recently developed Occupational Safety and Health Administration method for flavorings by gas chromatography-mass spectrometry using a different extraction solvent has been investigated in FY 2017. In addition, a new sampler that can distinguish flavorings present in air as vapors, particle-bound flavorings, and vapors off-gassing from collected particles has undergone evaluation with diacetyl and has performed well. |
| Nanoaerosol monitoring methods<br><br>Study Scientist: Eileen Birch | Development and application of measurement methods for hazardous aerosols. Globally, exposure to hazardous aerosols remains a serious health concern, with growing attention on fine, ultrafine, and nanosized aerosol particles. New nanomaterials are being developed and used in multiple commercial products, but their health and environmental impacts are little known. Multiple analytical tools are being used because the properties most responsible for nanoaerosol toxicity are unclear and exposures to complex mixtures often occur. This research is providing critical exposure data and information on the widely differing physical and chemical properties of nanoscale aerosols and materials, properties which might influence particle toxicity. The methods have general application to exposure monitoring and control studies.<br><br>Metal content was determined by inductively coupled plasma atomic emission spectroscopy after microwave digestion in concentrated nitric acid. All materials were analyzed by thermogravimetric analysis, which gives the onset of oxidation (a measure related to stability) and residual ash content (a measure of purity). Most sample contained high concentrations, and the residual ash contents of the materials ranged from about 1 to 10%. Previously (FY 2016), polycyclic aromatic hydrocarbons and transmission electron microscopy analyses were completed. |

## Exposure Assessment

| Project & Study Scientist | Project Summary |
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| Exposure assessment for toxicologically important chemicals<br><br>Study Scientist: Brian Curwin | Characterization of workplace exposures to chemicals of toxicological concern as identified by NTP and NIOSH. Current studies evaluate welding fumes with emphasis on manganese, occupational exposure to carbon nanotubes and nanofibers, flame retardants, and polycyclic aromatic hydrocarbons in coal tar sealants. Goals of these studies include: (1) identifying industries, workplaces, uses, and users; (2) determining occupational health relevance; (3) estimating the number of workers exposed; and (4) conducting exposure sampling. |
| Industry-Wide Studies Branch research, development, and planning<br><br>Study Scientist: Elizabeth Whelan | Support of strategic planning and feasibility studies of high-priority issues and emerging problems in occupational health. |

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| Nanotechnology field evaluations<br><br>Study Scientist: Charles Geraci | Collection of information from as many different facilities in the field as possible regarding the (1) nature of engineered nanomaterials, (2) processes involved in the manufacture and use of nanomaterials, (3) potential worker exposures to nanomaterials, and (4) practices and control procedures in the workplace where nanomaterials are produced or used. As toxicology studies identify the biological hazards of nanomaterials, gaining a better understanding of actual workplace exposures is essential. |

## Immunotoxicity and Immunology

| Project & Study Scientist | Project Summary |
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| Immunotoxicological evaluation of occupational chemicals<br><br>Study Scientist: Stacey Anderson | Identification of occupational and environmental chemical hazards and evaluation of immune function and mechanisms associated with exposure. This research is contributing to better risk assessment and increased identification of immunological hazards encountered in the workplace, which ultimately will establish occupational exposure limits. |
| Identification of occupational allergens<br><br>Study Scientist: John Noti | (1) Identification of exposures to substances that can cause inflammatory or immune reactions in certain work environments. These exposures are important causes of occupational lung diseases, such as asthma and allergic alveolitis.<br><br>(2) Development of improved techniques for detecting such immune reactions before adverse clinical outcomes occur.<br><br>(3) Development of improved techniques for detecting and identifying inciting occupational agents.<br><br>This project is analyzing clinical samples, environmental bulk samples, and environmental aerosol samples. Successful completion of these investigations should lead to the development of effective prevention strategies for occupational allergies and asthma. |
| Characterization of in vivo protein haptenation following exposure to aerosolized 4,4'-methylene diphenyl diisocyanate<br><br>Study Scientist: Justin Hettick | Determination of the molecular targets of inhaled diisocyanate particulates and better understanding of the pathogenic mechanism of isocyanate-induced allergic disease. The project enhances the overall understanding of the fate of diisocyanate in vivo following occupational exposure by increasing our understanding of disease and identifying potential biomarkers of exposure. |

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| Exosomes as biomarkers and immune modulators of diisocyanate asthma<br><br>Study Scientist: Justin Hettick | Definition of mechanisms of occupational asthma associated with exposure to methylene diphenyldiisocyanate (MDI) by identifying biomarkers of MDI exposure and immune regulatory factors that influence the progression and severity of MDI-associated occupational asthma. Exposure to MDI, used in the manufacturing of glues and polyurethanes, results in occupational asthma in approximately 5–15% of workers. Currently, sensitive and reliable markers for MDI exposure and sensitization do not exist, partially due to the lack of specificity of markers commonly associated with asthma. Furthermore, the factors influencing susceptibility and severity of MDI-associated occupational asthma have not been elucidated. This project is identifying response and legacy biomarkers found in exosomes secreted into the bloodstream that would indicate isocyanate exposure and sensitization. Attempts are being made to distinguish chemically induced biomarkers from high-molecular-weight allergen-induced biomarkers and determine how exosome genetic content can influence asthma progression. The biomarkers identified in this study can be incorporated into a human exposome database and be used in future studies to distinguish MDI-associated occupational asthma from general environmental asthmas. |

## Genetics

| Project & Study Scientist | Project Summary |
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| Immunotoxicity of subchronic fungal exposures<br><br>Study Scientist: Brett Green | Determination of the pulmonary immunopathological outcomes of subchronic exposures to fungi nominated to NTP. Subchronic exposure studies with mycotoxin-producing strains of *Stachybotrys chartarum* and *Aspergillus versicolor* have been completed. Future subchronic exposure studies will focus on an atranone-producing strain of *S. chartarum*, *A. versicolor, A. alternate*, and fungi identified in NIOSH Health Hazard Evaluations and collaborative exposure assessment studies. Proposed studies will provide further insight into the mechanisms of pulmonary toxicity to fungi encountered in the workplace. |
| Immunomodulatory effects of triclosan on effector CD4 T cell development<br><br>Study Scientist: Nikki Marshall | Identification of the cellular and molecular mechanisms behind the immune-modulating effects of the antibacterial chemical, triclosan. This information is providing the basis for evaluating other nonsensitizing antimicrobial chemicals and helps identify potentially conserved mechanisms that contribute to allergic disease. Results of this project will help assess the need to evaluate these types of workplace chemicals, leading to better risk assessment and establishment of occupational exposure limits. |

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| Highly sensitive and practical biomarkers for nanotoxicity<br><br>Study Scientist: Pius Josephweb | Development, validation, and testing (using a rat model) of highly sensitive and minimally invasive biomarkers for early detection of pulmonary toxicity potentially associated with exposure to toxic nanomaterials. Techniques are being employed to develop transcriptomic signatures in blood as surrogate biomarkers for the pulmonary toxicity induced by inhalation exposure to specific nanomaterials. Bioinformatic analysis of the global transcriptomics data is being conducted to gain insights into the molecular mechanisms underlying the pulmonary toxicity of nanomaterials. Determining the molecular mechanisms of pulmonary toxicity and developing highly sensitive and minimally invasive biomarkers for nanotoxicity have implications in monitoring workers for their risk of developing adverse health effects potentially associated with exposure to toxic nanomaterials.<br><br>Results obtained from preliminary studies demonstrated that rats exposed to multiwalled carbon nanotubes (MWCNTs) can be distinguished from those exposed to crystalline nanocellulose using blood gene expression profiles. |
| Toxicological investigations of nitrogen-doped multiwalled carbon nanotubes<br><br>Study Scientist: Dale Porter | Examination of the potential effect of altering the chemical composition of MWCNTs on their bioactivity in vivo. Knowledge of doping modification could allow for the development and use of MWCNTs with reduced bioactivity, which might help reduce the hazard from workplace exposures. Such information might enable material scientists to incorporate a prevention-through-design philosophy into the development of new nanoparticle-based technologies using nanomaterials that pose lower risks to human health. These data contribute to NIOSH's effort to develop and implement an evidence-based strategy for recommending occupational exposure limits or occupational exposure bands for carbon nanotubes. These studies are comparing two MWCNTs with different chemical compositions: MWCNTs and nitrogen-doped MWCNTs. These studies should increase our understanding of the toxicological mechanisms responsible for MWCNT-induced pathologies and could help identify extrapulmonary sites of toxicity resulting from systemic transport of MWCNTs after pulmonary exposure. |
| Neurological risks associated with workplace chemicals and nanomaterials<br><br>Study Scientist: Krishnan Sriram | Evaluation of potential neurotoxicological effects associated with exposure to chemical agents, incidental nanoparticles, and engineered nanomaterials in experimental models. This study includes identifying hazards, evaluating molecular mechanisms of neurotoxicity, and identifying potential biomarkers of neurotoxicity. Findings from this study could contribute to the development of novel biomarkers for monitoring exposures and health effects, pre-job planning protocols, hazard and risk assessment paradigms, and occupational safety standards for neurotoxic exposures. |

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| Mechanism of carbon nanotube-induced carcinogenesis and aneuploidy<br><br>Study Scientist: Linda Sargent | Investigation of the relationship between carbon nanotube diameter and mechanism of carcinogenesis and aneuploidy. In vitro exposure of human cells to 1- to 4-nm-diameter single-walled carbon nanotubes disrupts the mitotic apparatus, resulting in errors of chromosome number. Data comparisons with 10- to 20-nm-diameter MWCNTs suggest the diameter of the nanotube is important in the genotoxic response and that carbon nanotubes are potentially carcinogenic. In a study in which MWCNTs were inhaled using a two-stage initiation and promotion model, 49-nm-diameter MWCNT not only disrupted the mitotic spindle pole but also disrupted the center of the chromosome. Previous work has demonstrated that MWCNTs are strong promoters of mouse lung adenocarcinoma. Ongoing research investigates the dose-response relationship of lung tumor promotion in a mouse model. |
| Epigenetic changes in response to nanoparticle exposure<br><br>Study Scientist: Min Ding | Investigation of potential pulmonary carcinogenesis in response to tungsten carbide-cobalt (WC-Co) particle exposure using cell culture and animal models. Mechanistic investigations, including gene mutation, activation of transcription factors, and reactive oxygen species generation, are being conducted to explain the events of WC-Co-induced tumor initiation, promotion, and progression. Determining the mechanisms involved in WC-Co-induced carcinogenesis and elucidating target-signaling pathways could provide insights for the development of biomarkers and possible prevention strategies for WC-Co-induced diseases. |
| Nano-metal oxide property affecting fibrogenesis or carcinogenesis<br><br>Study Scientist: Liying Rojanasakul | Investigation of the properties of nano-metal oxides that affect their fibrogenicity or carcinogenicity. Metal oxide nanoparticles are increasingly used in a variety of applications having the potential to release particles into the workplace air. Limited published studies using animal models have shown lung inflammation and fibrosis with pulmonary exposure to metal oxide nanoparticles at human exposure-relevant doses. This project is determining the effects of physicochemical properties (size and coating) on metal oxide nanoparticles toxicity and the underlying mechanisms. Results thus far have shown that cerium oxide nanoparticles in mice cause lung inflammation that is particle-size dependent. In addition, consistent fibrogenic effects from cerium oxide nanoparticles are observed in vitro and in an animal model. These results support the development of an economical in vitro tool for predicting the potential toxicity of metal oxide nanoparticles in vivo. Low-dose/long-term in vitro exposure models have been continually tested using several well-characterized metal oxide nanoparticles and human lung cells to determine metal oxide nanoparticle-type-dependent neoplastic transformation induction and mechanism, including ferric oxide nanoparticle-disrupted iron homeostasis. Silicon dioxide coating of the ferric oxide nanoparticle partially ablated such effects and could support potential safe-by-design strategies. |

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| Hydraulic fracturing: toxicological effects of silica and diesel exhaust exposure<br>Study Scientist: Jeffrey Fedan | Study of toxicological effects associated with hydraulic fracturing silica exposure and diesel exhaust exposure. The toxicities of inhaled hydraulic fracturing sand dust—alone and in combination with inhaled diesel exhaust to mimic worker exposures during hydraulic fracturing operations—are being studied. Effects of exposure on the lung, cardiovascular system, immune system, brain, skin, and blood are being examined using a battery of in vivo and in vitro experiments. The initial exposures to hydraulic fracturing sand dust, using two exposure doses, are completed. Exposures to diesel exhaust from a type II diesel engine are underway. Inhalation exposures to fracturing sand dust in combination with diesel exhaust also will be assessed. |
| Pulmonary function and nanoparticle inhalation: in vivo and in vitro effects<br>Study Scientist: Jeffrey Fedan | Characterization of MWCNT effects on critical aspects of lung function in vivo and airway function in vitro and provision of metrics to enable risk assessment strategies. In vivo experiments have demonstrated changes in pulmonary function and airway reactivity in animals exposed to MWCNTs. A comparison of the relative pulmonary toxicities of pristine and nitrogen-doped MWCNTs is underway. |
| Health effects of inhaled crude oil<br>Study Scientist: Jeffrey Fedan | Design and building of an inhalation exposure system that delivers crude oil vapor to rats. This system is being used to study the effects of crude oil vapor inhalation on the lung, cardiovascular system, immune system, brain, skin, and blood. Surrogate oil for the Macondo well in the Gulf of Mexico is being used. Acute inhalation exposures have been completed, and subchronic exposures are in progress. |
| Toxicity assessment of carbon nanotubes and carbon nanofibers from U.S. facilities<br>Study Scientist: Aaron Erdely | Evaluation of the toxicity of carbon nanotubes and carbon nanofibers obtained from U.S. facilities. To date, few studies have examined the toxicity of such a broad range of materials collected from manufacturing facilities with direct relevance to U.S. worker health. This study is assessing general pulmonary and systemic toxicity, pathology, biodistribution, and genotoxicity. |
| Toxicity associated with the life cycle of carbon nanotubes<br>Study Scientist: Aaron Erdely | Investigation of carbon nanotube toxicity at different stages of production. In vivo and in vitro data suggest that exposure to carbon nanotubes has significant adverse health effects. Few data are available to define the toxicity of carbon nanotubes at each stage of the production life cycle (as produced, post-production modification, and incorporation into composites), although the numbers of potentially exposed workers increases with each stage. This project is evaluating the pulmonary response and genotoxicity of carbon nanotubes at different stages of production. |
| A translational in vitro approach to assess cardiovascular risk<br>Study Scientist: Aaron Erdely | Development of an in vitro model to assess cardiovascular risk from particulates. Respiratory exposure to particulates has been associated with increased mortality from cardiovascular diseases. This project is developing and testing an in vitro model to assess cardiovascular risk following pulmonary exposure to engineered nanomaterials. |

# NTP at NIOSH: Immunotoxicology Research

## Interagency Agreement on Immunotoxicology Research

The NIEHS and NIOSH interagency agreement provides for support of NTP hazard identification activities aimed at preventing diseases or adverse effects caused by environmental exposure to chemical or physical agents. These cooperative studies continue to improve risk assessment by measuring what constitutes an adverse health effect on the immune system in humans. The FY 2017 studies listed below evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases.

## Immunotoxicology Studies

| Project & Study Scientist | Project Summary |
|---|---|
| Identification and characterization of cross-reactive fungal biomarkers<br>Study Scientist: Brett Green | Development of monoclonal and polyclonal antibodies to recombinant fungal biomarker antigens. The utility of these antibodies is important for quantifying occupationally relevant fungal biomarkers, particularly to those fungi nominated to NTP. |
| Toxicity of subchronic fungal exposures<br>Study Scientist: Brett Green | Characterization of the toxicological and pulmonary immune responses associated with subchronic fungal exposures using a model that replicates human exposure. This model uses an acoustical generator system and nose-only exposure chamber to characterize toxicological endpoints following subchronic exposures to spores derived from fungi nominated to NTP. Subchronic exposure studies with *Aspergillus fumigatus*, two mycotoxin producing strains of *Stachybotrys chartarum*, and *A. versicolor* have been completed. Future subchronic exposure studies will focus on an atranone-producing strain of *S. chartarum*, *A. versicolor, Alternaria alternata*, mixed fungal exposures, and other occupationally relevant fungi identified in concurrent NTP-funded diversity studies. Proposed studies will provide further insight into the mechanisms of pulmonary toxicity due to fungi encountered in the workplace. These toxicological studies will provide novel data sets that will be used to characterize the hazards that fungal exposure might present to human and occupational health. |
| Identification and characterization of fungal exposures<br>Study Scientist: Brett Green | Investigation and characterization of the diversity of mold in indoor and occupational environments using internal transcribed spacer region sequencing. In collaboration with intramural and external stakeholders, results from these studies have provided new insight into the complex diversity of mold present in these environments. This methodological approach has been used to support NIOSH Health Hazard Evaluations to characterize microbial hazards in the workplace. |

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|---|---|
| Analysis of mycotoxins in dust samples from a water-damaged building<br><br>Study Scientist: Robert Park | Examination of effects of exposure to fungal secondary metabolites, including mycotoxins, on occupant health in water-damaged buildings. Cost-effective and robust methods have been developed using ultra-performance liquid chromatography-tandem mass spectrometry for simultaneous analysis of 31 fungal secondary metabolites in environmental samples. The accuracy of the method has been improved by using eight isotopically labeled ($^{13}$carbon) mycotoxin internal standards to compensate for extraction loss and matrix effects. The developed method has been applied to (1) examine stability of secondary metabolites in spiked dust stored at different temperature conditions with 7 different points of time over 2 years, (2) analyze 500 dust samples collected from our Philadelphia School Study, and (3) quantify 2 mycotoxins (macrocyclic trichothecenes and sterigmatocystin) in air and culture samples from the subchronic animal exposure studies of *S. chartarum*, and *A. versicolor*. Future studies will (1) examine stability of standard materials of fungal metabolites stored in a freezer for over a year; (2) in collaboration with a research group in Austria, screen more than 550 microbial metabolites in dust samples collected from four water-damaged buildings in different areas in the United States; and (3) examine the effect of exposure to fungal secondary metabolites on occupant health using statistical models adjusted for exposures to other microbial agents also measured in the epidemiological studies. |

# NTP at NIOSH: Occupationally Relevant Exposures

## Comprehensive Assessment of Occupationally Relevant Exposures

NIEHS is coordinating an NTP effort with NIOSH to better understand worker exposures, identify occupational health research gaps, and educate workers. The NIEHS and NIOSH interagency agreement supports these projects. The FY 2017 efforts listed below address worker exposures to welding fumes, nanosized materials, food flavorings, and other industrial chemicals.


**NIOSH mobile lab for field studies**

## Occupationally Relevant Exposures

| Project & Study Scientist | Project Summary |
|---|---|
| Administrative support<br>Study Scientist: Elizabeth Whelan | Support of NIOSH scientists in (1) participating in review and oversight of NTP activities and (2) attending NTP-related meetings in Research Triangle Park, North Carolina and Washington, D.C. |
| Occupational exposure assessment of welding fumes with emphasis on manganese compounds<br>Study Scientist: Kevin Hanley | Characterization of welding fume exposures with a focus on manganese. Welders' exposures to total and respirable manganese were evaluated using a novel sequential chemical extraction method to (1) identify industries, such as construction, shipbuilding, manufacturing companies, and unions, involved in welding operations for which the potential for substantial manganese exposure exists; (2) develop methods to identify manganese compounds and different oxidation states based on selective solubility with various welding fume matrices; and (3) characterize welding fume exposures based on welding-associated jobs, tasks, and processes. Three hundred full-shift worker-days were assessed during stick electrode welding, gas metal arc welding, flux cored welding, and gas tungsten arc welding in construction, refineries, heavy equipment, structural steel, shipyard, and appliance industries. To date, three manuscripts have been published (and a fourth has been submitted to a journal) that demonstrated excessive manganese exposures associated with welding fumes, often exceeding Threshold Limit Values of the American Conference of Governmental Industrial Hygienists (ACGIH TLVs) by an order of magnitude. |
| Exposure assessment of engineered nanoparticles<br>Study Scientist: Charles Geraci | Identification of workplaces engaged in the synthesis, manufacture, and use of engineered nanomaterials and characterization of workplace exposures to selected engineered nanoparticles. |
| Durability of nanoscale cellulose fibers in artificial human lung fluids<br>Study Scientist: Aleksandr Stefaniak | Investigation of the in vitro durability of nanocellulose materials in artificial lung fluids. Data generated from this study will be used to inform larger in vivo inhalation studies. |
| Assessment of occupational exposures to flame retardants<br>Study Scientist: Cheryl Estill | Assessment of exposure to nine alternative flame retardants plus a panel of polybrominated diphenyl ethers. Exposure has been assessed at 19 facilities involved in the manufacture, installation, or use of goods containing these flame retardants. Worksite categories included are manufacture of products that use flexible polyurethane foams; fabrication and manufacture of rigid polystyrene foam; cutting, installing, or spraying polyurethane foam insulation at construction sites; gymnasiums; nail salons; and the fire service industry. This study is comparing exposures among industries, processes, and tasks; determining the routes of exposure; and making recommendations to reduce exposures. These data will be used to determine exposure levels of workers in different occupations and how they relate to the general population by comparison to the National Health and Nutrition Examination Survey data. The results will aid in the design, understanding, and use of toxicological studies and risk assessment. |
| Assessment of occupational exposure to polycyclic aromatic hydrocarbons (PAHs) in coal tar sealant applications | Evaluation of the levels of occupational chemical exposure among workers who are using coal tar-based pavement sealants. Coal tar is sometimes used as a base material for blacktop pavement sealants, accounting for as much as 35% of the formulation in some |

| Project & Study Scientist | Project Summary |
|---|---|
| Study Scientist: Kevin Hanley | of these products. Coal tar is a byproduct of the production of coke, which is needed for steel production. Coal tar pitch volatiles are a mixture of chemicals that can evaporate into air from products containing coal tar, including coal tar pavement sealants. Coal tar sealant aerosols and volatiles contain several chemicals known as PAHs. This study focuses on the assessment of occupational exposure to PAHs among coal tar sealant workers. Currently, no data are available in the scientific literature on exposure to PAHs and their metabolites for workers applying coal tar sealant-based coatings on pavements. This study is providing data regarding levels of exposure to airborne chemicals for comparison to current NIOSH recommended exposure limits, if available. Results for specific PAH chemicals using NIOSH analytical methods will be reported. PAHs are measured in dermal wipe samples, and PAH metabolites measured in biological samples collected from workers to characterize levels present in this workforce. In FY 2017, construction surveys increased the database by 968 PAH measurements for air exposure time-weighted-average calculations, 968 skin wipe PAH measurements; and 704 PAH metabolite analyses in urine specimens. |